Natural course and long-term prognosis in idiopathic Normal Pressure Hydrocephalus

– the effect of delayed surgery and clinical factors on outcome and survival

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Lennart Hellsing

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Abstract

Idiopathic Normal Pressure Hydrocephalus, iNPH, causes gait and balance difficulties, urinary incontinence and cognitive decline in mainly older persons and is treatable by insertion of a cerebrospinal fluid diverting shunt. The effects of postponing treatment in these patients have have been largely unknown and the benefits of treatment in the long-term, mortality and causes of death have not been reported in any large cohort of patients. The aims of this thesis were to study the natural course in untreated iNPH patients, and the effect of postponed treatment, with regard to outcome and survival. Moreover, the aim was to study the long-term outcome and survival in a large unselected cohort of iNPH patients treated all over Sweden, registered in the Swedish Hydrocephalus Quality Registry, SHQR.

A group of patients diagnosed with iNPH who due to capacity problems had to wait median 13 months for shunt surgery, was studied and compared to a group of patients operated without delay. Symptoms progressed during the wait. Once treated, these patients improved, but outcome was less beneficial than in the patients operated without delay (*paper I*). Their mortality was more than two-fold increased (*paper II*). In 979 iNPH patients from the SHQR, around 60% stated being improved 2 to 6 years after shunt surgery. Re-operations were necessary in 26% but did not influence the long-term outcome, and vascular comorbidity had only minor effects (*paper III*). Survival was reduced compared to the general population, and shorter in patients with more pronounced symptoms or with heart diseases. Patients with the most beneficial treatment effects, survived similarly as the general population. Death due to cerebrovascular diseases was more common in iNPH patients, while death due to malignancy was less common, than in the general population (*paper IV*).

This thesis indicates that the natural course of iNPH is progression of symptoms which are only partially reversible and in order to optimize treatment benefits and survival, surgery should be performed without delay. The majority of this aged patient group, also those with vascular comorbidities, have favourable long-term effects and should also be offered treatment. Complications are common, but do not seem to hamper the long-term results. Treatment improves the symptoms and increases survival in iNPH.

Keywords:
Normal pressure hydrocephalus, Gait disorders, Cognitive disorders, Natural history, Prognosis

Sammanfattning på svenska

Vid idiopatisk normaltryckshydrocefalus, iNPH, en neurologisk sjukdom som företrädesvis drabbar äldre personer, är hjärnans kammarsystem förstorat av okänd orsak. Sjukdomen ger upphov till gång- och balansrubbning, urininkontinens och kognitiv svikt eller demens. Behandling via neurokirurgisk shuntoperation – där en tunn slang opereras in för att kontinuerligt leda bort överflödig hjärnkammarvätska antingen till bukhålan eller hjärtat - gör att 80% av patienterna förbättras. Avhandlingen studerar effekten av fördröjd behandling på sjukdomsutveckling, behandlingsresultat och överlevnad. Den studerar även flera olika faktorers betydelse för behandlingsresultatet och överlevnaden på lång sikt.

Patienter som behövde vänta i mediantal 13 månader på operation, försämrades under väntetiden. De förbättrades när de väl opererades, men blev inte lika bra som en tidigt opererad grupp patienter (*delarbete I*). Vidare, hade patienterna med fördröjd behandling mer än dubbelt så hög dödlighet på 5 års sikt (*delarbete II*). Av närmare 1000 opererade patienter från Nationellt Kvalitetsregister för Hydrocefalus angav c:a 60% att de fortfarande var förbättrade 2–6 år efter operationen. Samtidig hjärtkärlsjukdom hade endast begränsad negativ inverkan. Även om än 1 av 4 drabbades av komplikationer till shuntoperationen, påverkade detta inte behandlingseffekten på längre sikt (*delarbete III*). iNPH-patienter hade nästan dubbelt så hög dödlighet jämfört med normalbefolkningen och dödligheten är högre hos patienter med kraftigare symtom. Däremot sågs ingen ökad dödlighet hos de patienter som hade bäst effekt av shuntoperationen. Jämfört med normalbefolkningen var det dubbelt så vanligt att patienterna med iNPH dog av stroke, medan död till följd av tumörsjukdomar var ovanligt (*delarbete IV*).

Avhandlingen visar att shuntkirurgi är en effektiv behandling vid iNPH som gör att majoriteten av patienterna mår bättre och lever längre. Obehandlat leder sjukdomen till gradvis försämring. Skyndsam operation ger ett bättre behandlingsresultat och minskar risken för förtidig död. Långtidsresultatet är bra även hos patienter med hjärtkärlsjukdom, vilka också bör erbjudas behandling. Det är viktigt att informera patienter om risken för komplikationer, även om dessa inte påverkar resultatet på lång sikt.

List of papers

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

I. Andrén K, Wikkelsö C, Tisell M, Hellström P.

Natural course of idiopathic normal pressure hydrocephalus

Journal of Neurology, Neurosurgery and Psychiatry 2014 Jul; 85: 806-810.

II. Andrén K, Wikkelsö C, Hellström P, Tullberg M, Jaraj D.

Early shunt surgery improves survival in idiopathic Normal Pressure Hydrocephalus

Submitted.

III. Andrén K, Wikkelsö C, Sundström N, Agerskov S, Israelsson H, Laurell K, Hellström P, Tullberg M.

Long-term effects of complications and vascular comorbidity in idiopathic normal pressure hydrocephalus: a quality registry study

Journal of Neurology 2018 Jan; 265: 178-186

IV. Andrén K, Wikkelsö C, Sundström N, Agerskov S, Israelsson H, Laurell K, Hellström P, Tullberg M.

Survival in treated idiopathic normal pressure hydrocephalus

Journal of Neurology 2020 Mar;267(3):640-648.

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Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
Aβ	Amyloid β
CDR	Cause of Death Registry
CI	Confidence interval
CSF	Cerebrospinal fluid
CSF-TT	Cerebrospinal fluid tap test
ELD	Extended lumbar drainage test
HR	Hazard ratio
ICP	Intracranial pressure
iNPH	idiopathic Normal Pressure Hydrocephalus
IQR	Interquartile range
LP	Lumbo-peritoneal
MMSE	Mini-mental State Examination
mRS	modified Rankin Scale
NPH	Normal Pressure Hydrocephalus
NPV	Negative Predictive Value
OR	Odds ratio
PPV	Positive Predictive Value
SDH	Subdural haematoma
SHQR	Swedish Hydrocephalus Quality Registry
SMR	Standardized mortality ratio
smRS	self-assessed modified Rankin Scale
sNPH	secondary Normal Pressure Hydrocephalus
VA	Ventriculo-atrial
VP	Ventriculo-peritoneal
WMLs	White matter lesions

1. Introduction

1.1 Normal pressure hydrocephalus

1.1.1. Nomenclature and history

Hydrocephalus (from the Greek *hydor*, water and *kephale*, head), is a term for conditions with increased amount of cerebrospinal fluid (CSF) within the cranium, causing the brain's ventricles to enlarge. Hydrocephalus can be either *obstructive,* due to obstructions of the passage of CSF between the brain's ventricles, or *communicating,* without obstructions. Obstructive hydrocephalus is most commonly caused by acute or subacute disease processes, such as intracerebral haemorrhages or brain tumours giving rise to acute symptoms: headache, nausea, vomiting and unconsciousness. In these conditions the intracranial pressure (ICP) is high. There are also chronic forms, due to narrowing of the passages between the ventricles, most commonly the aqueduct. Communicating hydrocephalus on the other hand, gives rise to *normal pressure hydrocephalus,* NPH, where the ICP is within normal range. This condition presents with insidious gait and balance difficulties, bladder symptoms and cognitive symptoms. Headache is less common.

Normal pressure hydrocephalus can arise secondarily to other disease processes: intracranial haemorrhage, meningitis or trauma – then termed secondary NPH, sNPH. The other, more common form, which is the topic of this thesis, arises primarily in older persons, of unknown cause: idiopathic NPH, iNPH.

The phenomenon that hydrocephalus also with normal ICP can be treated by CSF diversion was first discovered by the Colombian neurosurgeon Salomon Hakim in 1957. The first case was a 16-year-old boy who was initially improving after a severe head trauma, but was during the following weeks progressively semi-comatose. His ventricles were enlarged, and although ICP was normal (15 cmH_2O), he was awakened and able to speak after removal of 15 ml CSF via lumbar puncture (LP). Repeated LPs were performed, followed by insertion of a ventriculo-atrial shunt, resulting in complete recovery and return to school after 3 months[1].

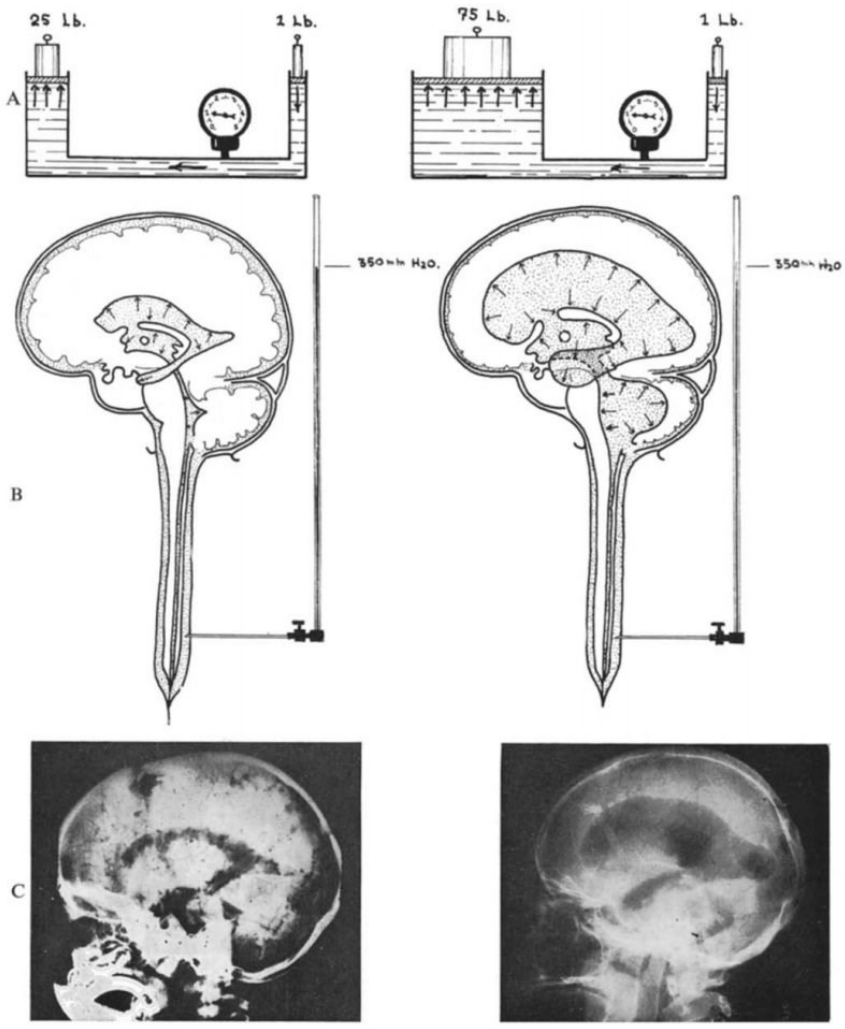

***Figure 1**: A) The relation of the CSF hydrodynamics to the physical principle involved is shown. A pressure of one pound is supporting three times the weight acting on a larger surface area. B) The same principle applies to the ventricular system. C) Corresponding pneumoencephalographic x-ray images.*
Reprinted from Journal of the Neurological Sciences, 1965;2:307-327, Hakim et al: The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal pressure. Observations on cerebrospinal fluid hydrodynamics, copyright (1965), with permission from Elsevier.

Having become aware of the notion of possibly reversible symptoms in spite of normal ICP in persons with communicating hydrocephalus, Hakim discovered several older persons with similar symptoms of gait and balance difficulties, urinary incontinence and dementia who improved after CSF diversion. In a

landmark paper in 1965[2], he presented a case series of three persons in their 60s presenting with this syndrome and returning to normality after CSF drainage. For the first time, symptoms primarily caused by the hydrocephalic state in itself could be discerned; the combination of gait, cognitive and bladder disturbances, often referred to as "Hakim's triad". He explained the phenomenon of a normal pressure maintaining the enlarged size of the ventricles by Pascal's law of physics: Force = Pressure x Area; meaning that when the surface area of the ventricles is large, a low pressure is enough to exert a great force on the ventricle walls (figure 1). Further, he found that the largest parts of the ventricles, i.e. the frontal horns, dilate the most – giving rise to frontal lobe dysfunction.

He foresaw and discussed the difficulties in differential diagnostics versus primarily other types of dementia, in first hand Alzheimer's dementia and cerebrovascular disease. He also observed that the absence of effect of lumbar punctures did not rule out the possibility of improvement after permanent CSF diversion. Several of the clinical and scientific enigmas described by Hakim in the 1960s, still bewilder the scientific community.

1.1.2 Diagnostic criteria

There is no single test to diagnose a person with iNPH, instead the diagnosis is based on a combination of symptoms, evidence of typically enlarged ventricles, and a normal lumbar pressure. There are two sets of diagnostic criteria, the American-European published in 2005[3], which are applied in this thesis, presented in figure 2, and the Japanese, updated in 2012[4].

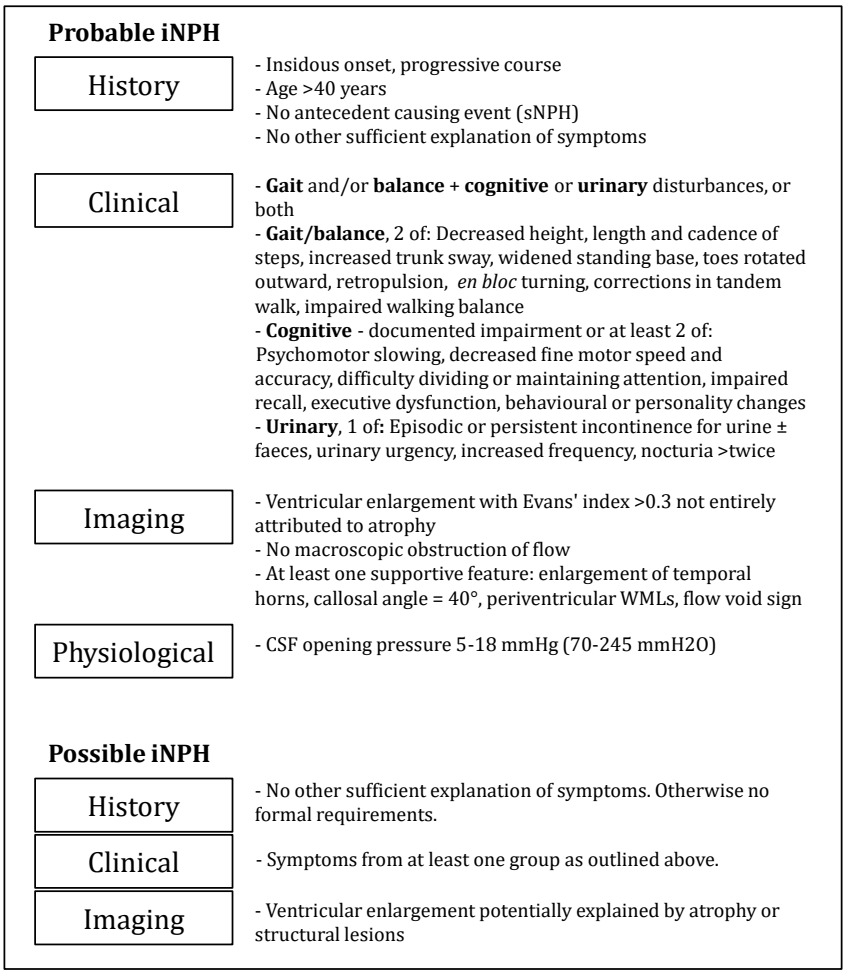

Figure 2: *Summary of diagnostic criteria for probable and possible iNPH, Relkin et al 2005*[3].

1.1.3 Demography

The prevalence of probable iNPH has been estimated to 10-22/100.000 inhabitants[5, 6], but with higher age-specific proportions of possible iNPH of 1.4-2.9% of persons aged 65 years or above in Japanese communities[7, 8]. In recent Swedish prevalence studies, the prevalence of probable iNPH was estimated to 2.1% (Jaraj[9]) and 3.7% (Andersson[10]) of persons aged ≥70[9] and ≥65[10] years. In the

same studies, the prevalence above 80 years of age, was as high as 5.9%[9] and 8.9%[10] respectively.
The incidence has been estimated to 5.5-11.9/100.000 inhabitants/year[5, 11, 12], again with higher numbers in higher age with 1.2/1000 inhabitants/year for persons aged 70 years or above[13].

Only the study by Jaraj[9] is population based from prospective cohort studies, while other studies are hospital, registry or survey based. A recent systematic review on the topic, concluded that the methodological and clinical heterogeneity of these studies does not allow for adequate conclusions on the prevalence or incidence rates.[14]

The incidence of surgery for iNPH - number of operated persons/100.000 inhabitants/year - has been reported to be 1.09 in Norway 2002-2006[15], 0.5 in the UK shunt registry 2004-2013[16], and 2.2 in the Swedish Hydrocephalus Quality Registry, SHQR, 2004-2011[17]. In Germany, persons with an insurance claim for the diagnosis of iNPH, were 1.36/100.000 inhabitants/year in 2012[18]. Although diagnosis and operation of iNPH is increasing[16-18], up to 3.4/100.000/year operated in 2011 in Sweden[17], a comparison with most prevalence and incidence studies suggests that iNPH is still underdiagnosed[19], and that only 20-30% receive treatment.

1.1.4 CSF circulation

The CSF has classically been believed to be mainly produced in the choroid plexuses located in the lateral, third and fourth ventricles, but is also derived from the brain parenchyma[20]. Approximately 500 ml per day is produced[21] and the total CSF volume is around 200 ml. Known functions include nutrient delivery, clearance of waste products, serving as a medium of chemical signalling and physical shock-absorbent protection, as the brain floats in this liquid. It also contributes to the regulation of intracranial pressure. Within the ventricular system, it has a pulsatile back-and-forth flow with each cardiac cycle. The net flow is directed from the lateral ventricles via the foramen of Monro to the third ventricle, further via the aqueduct of Sylvius to the forth ventricle and from there, through the foramina of Luschka and Magendie accessing the basal cisterns and the subarachnoid space of the brain and spinal cord[22]. Reabsorption routes have traditionally been said to be via the arachnoid villi to the venous blood primarily in the superior sagittal sinus – but an important amount has been found to be reabsorbed in the spinal canal[21], along blood vessels and cranial nerves[23].

Emerging data during the last years, have resulted in a paradigm shift in the view of CSF as being rather separated from the brain parenchyma not adjacent to ventricles. A close communication and exchange between the CSF, the blood and the interstitial fluid in the extracellular space (ECS) surrounding the brain's neurons has been discovered.[24-26] According to these findings, CSF flows, primarily during sleep, through the parenchyma via para-arterial passages (Virchow-Robin spaces), and passes the blood-brain-barrier of astrocytic end-feet surrounding the arteries, through Aquaporin 4 water channels[27]. CSF passes into the ECS and interchanges nutrients and metabolic waste products such as amyloid with the interstitial fluid. The interstitial fluid then flows further to para-venous passages, also through Aquaporin 4 water channels in the astrocytic end feet. This process is termed the *glymphatic* system, as it resembles a *lymphatic* system, mediated by *gl*ial cells (astrocytes). The flow through the interstitial space is thought to be an active bulk flow rather than diffusive, but this is still a matter of debate.[28]

A few studies have tried to capture signs of the hypothetically impaired glymphatic system in iNPH. MRI with intrathecal gadolinium contrast injection, showed reduced gadolinium clearance in a pattern interpreted as impaired glymphatic function in iNPH compared to controls.[29] In diffusion tensor imaging (DTI) which is a technique of measuring the direction of water molecule movements, an index for analysis along perivascular spaces could differentiate iNPH patients from controls and from other patients with ventriculomegaly.[30] This was also interpreted as showing impairment of the glymphatic system in iNPH patients. Moreover, the concentration of Aquaporin 4 is lower in the perivascular parenchyma of iNPH patients, constituting further support to glymphatic disturbance, thought to contribute to impaired clearance of toxic waste products and neurodegeneration.[31]

1.1.5 Pathophysiology

As *idiopathic* implies, there is not one specific known cause of iNPH – but many contributing causes and disturbed physiological processes are known. Neither are there specific post mortem pathological, nor in vivo brain biopsy findings. Leptomeningeal fibrosis, vascular and Alzheimer's Disease (AD) changes have been described, but none of these findings are specific for iNPH or seen in all patients [32], [33] [34] [35], [36].

Extensive findings support chronically altered CSF dynamics, including the kinetics and reabsorption of CSF[37], as shown in both hydrodynamic[38-40] and

neuroradiological[22] investigation methods, with e.g. increased resistance to outflow (R_{out}), increased amplitude of cardiac-related CSF pulsations in relation to ICP[38], and hyperdynamic CSF flow through the aqueduct[22].

Further there is an agreement of vascular involvement, on the arterial side[41], venous side[42] or both, supported among other findings, by the observed association of arterial hypertension and iNPH[43-46]. However, no prospective longitudinal study, confirming causality between these risk factors and iNPH, has been performed.

Processes theoretically involved are illustrated in figure 3. Altered arterial hemodynamics in systole, cause disturbances of CSF pulsations, leading to ventriculomegaly with mass effect, and periventricular oedema contributing to local ischemia with reduced CBF (cerebral blood flow) and lowered oxygen consumption[47]. Periventricular neural tracts and small blood vessels are affected and the glymphatic function is impaired[29-31], theoretically leading to reduced clearance of toxic waste products, contributing to neurodegeneration and disturbed autoregulation. Together these mechanisms result in cerebral dyshomeostasis, hypometabolism and neurotoxicity.[37]

The regions where disturbances are seen, are reflected by the symptoms they cause, mainly in the basal frontal lobes (cognitive and motor symptoms, micturition), periventricular areas and basal ganglia (motor symptoms), but also periaqueductal mesencephalic areas have shown to be affected[48] (pontine micturition centre, vestibular system for balance/posture, integration and interpretation of visual stimuli, reticular activating system).

The findings of AD-related changes in iNPH brain biopsies[49], and the partly similar clinical in vivo and post-mortem[50] presentations, have led researchers to believe that these two conditions were related or overlapping. However, more recent studies contribute to the conclusion that these two are separate disease entities. E g the ApoE Ɛ4 allele is not over-represented as in AD[51], the profile of amyloid-β (Aβ) fragments in CSF is different from AD[52] and the distribution of Aβ in iNPH patients' brains examined with amyloid PET imaging was different from AD patients[53]. Three out of ten patients had increased cortical amyloid, but while the distribution in AD is typically in the temporoparietal areas, the distribution in iNPH brains was limited to the high convexity parasagittal areas. Those regions might be mechanically more compressed, resulting in decreased clearance of Aβ.

At least a subset of patients is thought to suffer from a "2 hit" disease with congenital hydrocephalus in infancy, without functional implications during

childhood and younger adulthood but becoming symptomatic in older adulthood due to declining compensatory mechanisms[22]. This is supported by larger intracranial volumes and larger head circumference[54, 55] in persons with iNPH.

Familial aggregations of iNPH cases have occasionally been observed, indicating that unknown genetic factors may play a role[56, 57]. There is emerging evidence of a possibly genetic ciliary dysfunction being involved in the development of hydrocephalus, as ependymal cilia contribute to directing the movement of ventricular CSF[58, 59].

Moreover, neuroinflammatory and hormonal effects have been described, probably constituting secondary phenomena: increased CSF-IL-6 and IL-8[60] and increased S-IGF-I[61], known to play a role in endogenous brain damage response.

Finally, as illustrated in figure x, the pathophysiology should probably be seen as a multifactorial cascade of events, with a self-reinforcing circle of effects, and a final common pathway seen in the clinical presentation. The diversity and controversies in different studies about diagnostic investigations, possibly reflect investigations in different phases of the pathophysiological development – and/or diverse primary causes, perhaps motivating a better classification of the iNPH entity into subgroups.

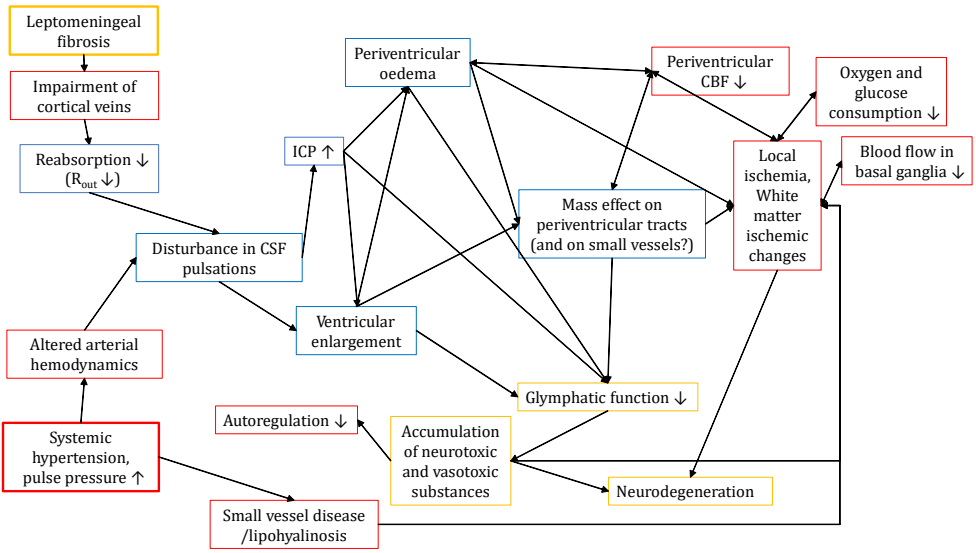

***Figure 3**: Pathophysiological processes hypothetically involved in iNPH.*

1.2 Symptoms and signs

"She moved slowly and her mind lost its quickness"[2]

A major challenge in diagnosing iNPH is that all hallmark symptoms are common in the older population and have many causes. Gait disturbance is seen in 20% of persons aged 75 years or above[62], dementia in 14% of persons 70 years or older[63], and urinary incontinence in 38% of women[64] and 17% of men aged 60 years or older[65]. Therefore, thorough characterizations and analyses of combinations of symptoms, are crucial.

1.2.1 Gait

> *"The unsteadiness of gait, which was difficult to characterize, was not only clearly ascribable to cerebellar deficit. Generally, function was more deranged in the lower limbs than in the upper."*[2]

As highlighted by the diagnostic criteria (figure 2)[3], the typical gait disturbance in iNPH is with a widened standing and walking base (seen in 75%[66]), short steps, shuffling (in 65%[66]), decreased step height and cadence. A gait analysis comparing iNPH patients to patients with Parkinson's disease and healthy controls, showed lower velocity and stride length in both Parkinson's and iNPH but iNPH patients stood out by a wider step width, foot angle with outward rotated toes during walking, and a lower step height[67]. In a Gothenburg study with symptom characterization of 429 iNPH patients, at the time of diagnosis symptoms ranged from normal or discrete disturbance of turning (requiring three steps or more to turn 180°) and tandem walking (heel-to-toe "on a line"), to complete inability to walk[66]. Specifically, the presence of shuffling, is prognostically significant, predicting better treatment outcomes[66].

1.2.2 Balance

Balance is thought to be separately affected in iNPH, with increased trunk sway and risk of falling, due to deficient central integration of vestibular function, not only as a part of gait disturbance[68, 69]. The disturbance has been found by some to be more responsive to treatment than the gait disturbance itself[69] but by others, found to be only slightly improved[68, 70]. iNPH patients have been found to be less

helped in their postural function by visual input, and experiments imply a misinterpretation of visual stimuli with inability to perceive the direction of vertical objects correctly, a disturbance assumed to be topically located in the brain stem, similarly as the vestibular disturbance mentioned above[71, 72]. In the study with Gothenburg patients, the median time achieved in Romberg's test was 20 s preoperatively, increasing to 60 s postoperatively. Retropulsion was seen in 46%, and in half as many after treatment[66].

1.2.3. Cognitive symptoms

> *"Lack of spontaneity and initiative, faulty concentration, distractibility, lack of interest, apathy and inertia (...) Inner psychic life seemed to be impoverished, and the patient bereft of thoughts."*[2]

The cognitive deficits in iNPH are often described as frontal-subcortical impairments[73]. Importantly, not all patients have dementia. Of the 429 Gothenburg patients, only about half had mild-moderate or severe dementia, defined as MMSE score ≤25, the other half had no or questionable dementia (MMSE >25)[66]. Most neuropsychological functions can be affected; most typically psychomotor speed, attention and concentration, memory and learning, and executive functions[74, 75]. The presence of anomia, should draw suspicion to a comorbid cortical neurodegenerative disease such as AD[76].

iNPH patients performed worse than healthy individuals in each one of a wide battery of neuropsychological tests, reflecting multiregional pathological changes and impaired connectivity[75]. The majority of these functions improve after shunt surgery, but do not normalize to the level of healthy individuals[77, 78].

An interrelated aspect or way to describe mental functioning is with the organic psychiatric syndromes where the somnolence-sopor-coma-disorder with impaired wakefulness is most commonly seen and best responsive to shunt treatment[79, 80]. The emotional-motivational blunting disorder is also common in iNPH, characterized by emotional bluntness, disinterest, passivity, and by impaired ability of planning, abstraction and self-criticism [79, 80]. The daily need for sleep is typically increased in iNPH patients, and was reduced from median 9h pre-operatively to 8h post-operatively, p=0.0001[66].

1.2.4 Urinary symptoms

Urinary urgency and/or incontinence is almost always present and needs to be carefully asked for as patients might not convey this symptom spontaneously[81, 82]. The typical dysfunction is that of an overactive bladder with increased frequency of voiding, involuntary premature detrusor contractions, and diminished storage capacity[83-85]. These symptoms are improved by shunt surgery in most patients[84]. Also voiding dysfunction with lower flow rates and residual amounts of urine post-voiding, is seen, but these dysfunctions were not seen to improve after treatment[84] probably representing other lower urinary tract disorders in older persons. The functional implications range from urgency or frequency of micturition, to incontinence of varying degree with the need of diapers, and in a small proportion of patients with more severe symptoms in general, also faecal urgency and incontinence can be seen[66].

1.2.5 Other symptoms and signs

Apart from gait and balance difficulties, more general motor impairment is seen in iNPH including the fine motor function of the hands[86, 87]. Bradykinesia, also in upper extremities, is seen in 50-68% of patients, and rigidity in 14-43%[88-90]. Parkinsonism according to the UK brain bank criteria (bradykinesia in combination with rigidity, rest tremor or postural instability), is seen in 71%[91]. In the Gothenburg study of 429 patients, paratonia in the legs was seen in 73%, and reduced to 59% post-operatively[66]. Focal neurological findings should not be seen as contradictory to the diagnosis, as such were seen in 25% of patients. Cerebellar ataxia was found in 12% and diminished to 7% post-operatively, possibly adding evidence to infratentorial involvement in the functional impairments[66]. Disinhibited primitive reflexes were seen in up to 84% of patients in another study[92].

In summary, the clinical syndrome is with gait and general motor impairments, defective postural functions, cognitive and bladder dysfunctions, and the symptoms are most commonly inter-related.

1.3 Diagnostic modalities

The diagnostic routines differ between centres, but are generally extensive and resource demanding. Still, after careful investigations, a beneficial outcome is seen in approximately 80% of treated patients, while the remaining 20% were exposed to surgical risks without benefits[93]. Continuous extensive research efforts are made to improve the diagnostic performance and to find investigation methods with high positive and negative predictive values. However, to date, no specific single test can adequately diagnose iNPH or predict treatment outcomes, probably contributing to rendering the condition underdiagnosed and undertreated.

1.3.1 Neuroimaging

As highlighted by the diagnostic criteria[3, 4], the most important part of the laboratory investigations is neuroimaging with CT or MRI showing morphological signs of an increased ventricular volume disproportionate to subarachnoid space volume, i.e. not due to atrophy, and without obstructions of CSF flow. The most commonly used indicator of enlarged ventricles is Evans' index[94], where the maximum width of the frontal horns is divided by the maximum inner width of the cranium in the same image. An Evans' index >0.3 is considered consistent with increased ventricular size, but it is important to note that this is regardless of the cause of large ventricles and is seen in 20% of persons aged 70 years or above[95]. The Japanese described a typical pattern of morphological changes in iNPH termed DESH for *disproportionately enlarged subarachnoid space hydrocephalus*, a combination of narrow medial subarachnoid spaces, tight high convexity sulci, dilated Sylvian fissures, and ventriculomegaly[96]. Focally enlarged sulci are seen in 25%[97-99]. The corpus callosum angle is another morphological marker found useful in distinguishing hydrocephalic ventricular enlargement from atrophy, with the most commonly used cut-off of <90°[100]. Further, widening of the temporal horns not due to hippocampal atrophy is another potentially useful marker[101]. All mentioned morphological markers together with periventricular hypodensitites are included in the recently published RadScale, a composite score constructed to grade the typical findings of iNPH[98]. The morphological markers can support but should not be obligatory for the diagnosis, as they are not seen in all patients and the predictive value of has been investigated with conflicting results[99, 101, 102]. Some morphological signs are illustrated in figure 4.

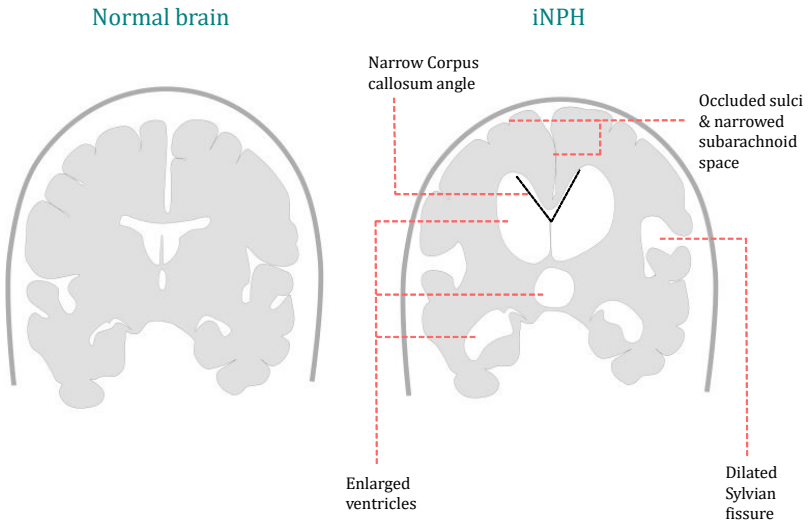

Figure 4: *Morphological findings in iNPH.*
Reprinted with permission from Dr Daniel Jaraj

A flow void sign, obtained by MRI technique, is commonly seen in the cerebral aqueduct and/or fourth ventricle, and helps to exclude obstruction in these sites[103]. It has been perceived as typical for iNPH and included as a supportive criterion[3], but has a low specificity and no predictive value[104]. Another, more reliable way of verifying communications between ventricles is by radionuclide cisternography, which in addition has a typical pattern of high ventricular activity in the majority of iNPH patients[105].

White matter lesions, WMLs, seen as both periventricular (PVH) and deep white matter hyperintensities (DWMH), are best visualized by MRI but also seen on CT images. These are common findings in iNPH and less common in healthy controls[106, 107]. They are associated with vascular risk factors[108] and thought to be caused by microvascular ischemia, possibly in combination with periventricular oedema[107, 109]. Even severe WMLs do not contradict the potential of improvement by shunt surgery[110], and the extent of PVH may be reduced after surgery, correlating to the degree of clinical improvement[111].

Several methods of cerebral blood flow or perfusion measurements - SPECT, PET and various CT and MRI based techniques - have shown global or locally reduced perfusion in periventricular white matter, basal ganglia, medial frontal cortex, cingulate gyrus, the hippocampus and in the mesencephalon, in many studies observed to improve after shunt surgery[112-118]. Glucose uptake visualized by ^{18}F-FDG-PET/CT is reduced in the basal ganglia but preserved in the cortex[119].

Further, used for research purposes, diffusion weighted imaging (DWI) with increased ADC in periventricular white matter reflecting increased extracellular water content has been seen in several studies, with ADC decreasing postoperatively[112, 120]. Diffusion tensor imaging (DTI) has shown lower water diffusivity around the ventricles, in a pattern interpreted as partially reversible stretch/compression of periventricular neural tracts[121].

Lastly, other isotope imaging techniques that have been investigated include amyloid-PET methods, mainly for differential diagnostic purposes, revealing Alzheimer pathology with important consequences of expected outcomes[53, 122, 123]. Similarly FP-CIT SPECT (DaT-scan) could be helpful for discrimination between iNPH and neurodegenerative dopaminergic disorders with similar symptoms[124], as dopaminergic deficiency post- but not pre-synaptically has been seen in iNPH patients[125]. It must be noted however, that comorbidity of AD or neurodegenerative movement disorders with iNPH are possible.

1.3.2 Hydrodynamic investigations

CSF infusion tests[126], where saline is infused through a lumbar puncture, while the intrathecal pressure is monitored, are used to calculate the resistance of CSF outflow in the central nervous system, termed R_{out}. It is widely used for supplementary testing and selection of surgical candidates, as a higher R_{out} is associated with a higher probability of good response to shunt surgery[127] . However, there is no threshold below which a shunting effect can confidently be ruled out[128]. Neither does the test accurately separate iNPH patients from controls: an R_{out} of >12 mm Hg/min/ml is seen in 83% of iNPH patients[129], but also in 25% of healthy older controls[130].

Continuous intraventricular or lumbar ICP monitoring to determine the frequency of typical ICP curve findings of A and B waves or pulse amplitudes were not supported by the iNPH guidelines[127].

1.3.3. Functional tests with CSF removal

Supplementary tests in which some amount of CSF is removed, can aid in predicting which patients, and in what way patients will benefit from shunt surgery[78, 127]. For the CSF tap test (30-)50 ml of CSF is removed by lumbar puncture and the patients' symptoms are assessed before and after the tap[131] . Such testing provided good positive predictive values (PPV) of 73-100% in eight studies reviewed in 2016[132]. However, the negative predictive value (NPV) was only 18-50%[132], meaning that also patients with a negative tap test might improve after shunting and the test cannot be used to rule out patients from treatment[127, 128]. The extended lumbar drainage (ELD) test involves continuous CSF drainage during 72 h via a lumbar intrathecal catheter[133]. Neither can this test rule out the possibility of response to shunt surgery if negative - the PPV of the ELD ranges between 80-100%, and the NPV between 36-100 in three studies[133-135].

1.3.4 CSF biomarkers

All amyloid precursor proteins and amyloid β fragments of different lengths (Aβ-38, -40, and -42) are lower in iNPH than in healthy controls[52, 136]. This is contrary to AD where specifically Aβ-42 is low in CSF, thought to reflect defective turnover of this protein which instead aggregates, forming amyloid plaques in the brain parenchyma[137]. The levels of Tau proteins – Tau and phosphorylated Tau (p-Tau), indicating cortical neuronal damage, are normal or slightly reduced, as opposed to the findings in AD where levels are typically higher than in healthy controls, and these markers have been pointed out by a recent systematic review as having the best potential of differentiation between iNPH and AD[138]. Neurofilament light, NFL, a marker of damage to myelinated axons, is slightly elevated[52, 139] in iNPH compared to controls.
A combination of Tau levels, MCP-1 (Monocyte chemoattractant protein-1), and Aβ-40 could be helpful to distinguish iNPH from conditions with partly similar clinical presentations: AD, vascular dementia, frontotemporal lobe dementia, Lewy-body dementia, Parkinson's disease, Progressive supranuclear palsy, Multiple system atrophy, and corticobasal syndromes [140].
Finally, CSF biomarkers have added to the understanding of the pathophysiology of iNPH and can contribute to the differential diagnostics between iNPH and similar conditions, but have so far not been found to be of predictive value[141].

1.4 Treatment and outcome

1.4.1 Treatment

The only evidence-based treatment is surgical placement of a CSF diverting shunt catheter[142]. Most commonly the proximal tip of the catheter is inserted into one of the lateral ventricles, and the distal end in the peritoneal cavity – ventriculo-peritoneal (VP) shunts. In patients with e.g. history of abdominal surgery or peritonitis with multiple peritoneal adhesions, or earlier failure of VP shunts, peritoneal placement can be inappropriate and the distal end can instead be placed in the right atrium of the heart – ventriculo-atrial (VA) shunts. In lumbo-peritoneal (LP) shunts, the proximal end is placed within the dura mater of the spinal canal, and the distal end in the peritoneal cavity. Other placements such as ventriculo-pleural are possible but less commonly used. A novel strategy evaluated in Japan with promising results, is lumbosubarachnoid-lumboepidural shunts[143]. In modern shunt systems widely used in iNPH patients, the proximal and distal catheters are joined by a differential pressure or flow regulated valve mechanism where the resistance to outflow can be adjusted by external devices, to balance the effect and side effects of treatment[142].

Endoscopic third ventriculostomy has also been employed for treatment of iNPH patients, but without therapeutic effect in some patients who then needed second line treatment with shunting[144].

Thus, shunting (VP, VA or LP) is the treatment of choice for iNPH[144], even if there is some evidence of limited response to pharmacotherapy by Acetazolamide, showing reduced periventricular hyperintensities and gait improvement in some patients[145, 146].

1.4.2 Outcome

In a systematic review by Toma, with a meta-analysis of 30 studies published 2006-2010, 81% of altogether 1573 patients improved 3 months after shunt surgery. Moreover, the systematic review shows that improvement rates have increased with the development of diagnostic and surgical techniques since the 1970s[93].

There is no consensus on how to report outcome and a wide range of outcome measures have been used, e.g. illustrated in the literature review of long-term outcome studies in tables 1A and 1B.

A European multicentre study[147] included 142 patients from 13 countries and showed a one-year outcome of 69% improved by at least one step on the modified Rankin Scale, mRS[148, 149], a general disability measure (described in chapter 3.2). In the same study 84% improved as measured by the iNPH scale developed by Hellström et al[150] (described in chapter 3.1). All symptoms are known to be improved to varying extent, but gait is often described as the most clearly improved domain[144]. In the European multicentre study, in the specific subscores of the iNPH scale, 77% were improved in gait, 56% in balance, 63% in neuropsychology, and 66% in urinary symptoms. The Japanese SINPHONI study, including 100 treated patients from 26 centers in Japan, similarly showed a one-year-outcome of 69% of patients improved on the mRS, and gait improvement was seen in 77%[96].

Further, health economy studies have shown that shunt surgery for iNPH is cost effective[151, 152] and reduces health care expenditures[153]. The health related quality of life has shown to improve with treatment[154], also in the long-term[155].

Although studies show benefit in a majority of patients, most studies have been non-blinded and not presenting control groups, leading only to recommendation level C for shunting in iNPH by the American Academy of Neurology[156]. Existing RCTs on shunting, not mentioned in those guidelines[156] are reviewed below, in 1.5.2.

1.4.3 Complications

Complications associated with shunting include infections, subdural hematomas, intracerebral haemorrhages, shunt obstruction or misplacement, over drainage headaches and epileptic seizures[142]. The systematic review by Toma[93] also looked into the reported frequency of different complications in studies on iNPH and found that these have decreased since the 1970s. In the 30 studies published 2006-2010, mortality was seen in 0.2%, subdural haematomas in 4.5%, intracerebral haemorrhages in 0.2%, infections in 3.5%, seizures in 0% and shunt revisions were performed in 13%. Subdural haematomas are the most important complications to consider, from the perspective of permanent morbidity[142]. Such were found in 10.4% of 1457 iNPH patients operated in Sweden 2004-2014, and 33.6% of those underwent surgical treatment. Being on antiplatelet therapy or

having the shunt set to an initially lower outflow resistance were risk factors for the development of SDH, along with male sex compared to female[157].

In another study, shunt revisions diminished from 21 to 9% during 1995-2004 and right frontal placement of the ventricular catheter and the use of adjustable shunt valves were associated with a lower risk of shunt revisions[158]. Antibiotic impregnated shunts have shown lower risk of shunt infections[159].

The frequency of complications in a national registry reflecting every-day routine care in iNPH patients, and their influence on the long-term outcome, has previously not been published.

1.4.4 Comorbidities

As iNPH affects the older age group, prone to other conditions, the list of comorbidities of possible relevance to patients can be made long, as well as the list of differential diagnoses. It is important to assess these comorbidities, for adequate diagnostics and prognostication, for evaluation of safely performing anaesthesia and surgery, as well as for improving patients' health by tending also to other conditions. Common comorbidities and differential diagnoses include musculoskeletal conditions, cerebrovascular disease as well as other cardiovascular disease, psychiatric conditions, dementias, neurodegenerative movement disorders and urologic conditions[160]. A task force initiated by the ISHCSF (International Society of Hydrocephalus and CSF related disorders) have formulated recommendations for how to deal with these comorbidities in the setting of evaluation for iNPH[160].

As mentioned, an over-representation of vascular risk factors and vascular comorbidities in iNPH patients compared to the general population has been shown, hypothetically of relevance to the pathogenesis[161]. That hypertension is common in these patients is well established[44, 45, 162-164]. iNPH patients also have a heavier burden of diabetes mellitus[43-45, 163-165], hyperlipidaemia, obesity[43], ischemic heart disease[44, 163, 164] and arteriosclerotic cerebrovascular disease[44] compared to control groups.

Less beneficial results in patients with signs of ischemic cerebrovascular disease were seen in some studies[166, 167], and others chose to exclude patients who had suffered strokes[168, 169]. However, as stated, other studies showed that good shunt response is seen also in iNPH patients with extensive presumed WMLs[110, 170], that radiological signs of cerebrovascular disease could not predict the outcome in

iNPH patients[111] and that the magnitude of improvement in patients with and without vascular comorbidities is the same[147].

Vascular risk factors and vascular comorbidities' influence on the long-term outcome has, however, not been thoroughly studied in a large cohort of patients without exclusion criteria.

1.5 Natural course

Once there is a treatment for a disease, the natural history is difficult to examine, as there are ethical concerns with withholding that treatment for research purposes. The way that NPH was first discovered, was by showing this condition is treatable – meaning that there are no historic cohorts or cases that have been diagnosed and followed up but not treated, as there are for other neurologic diseases e g MS or acute stroke.

1.5.1 Studies with follow-up of untreated patients

A few studies with objective outcome measures have included untreated iNPH patients. Two of these, Scollato[171] and Razay[172], studied patients who were diagnosed with probable iNPH, while another four reported follow-ups of patients who were not thought to benefit from shunt surgery, based on specific hydrodynamic investigations, constituting possible confounding factors: Savolainen[81], Pfisterer[173] and Brean[174, 175]. These were all included in a systematic review on the natural history of iNPH published in 2011[176].
These studies are summarized below, highlighting the numbers of untreated patients by bold text.

Scollato et al[171] presented a case series of **9** prospectively studied iNPH patients who refused shunt surgery, and they verified deterioration before or at their 24 months evaluation in all patients: 6 of 9 patients in a gait scale, 9 of 9 patients in urinary symptoms and 8 of 9 patients in MMSE. The aim of the study was to evaluate the development in aqueductal stroke volume by phase contrast MRI imaging, and this was shown to progressively increase as symptoms progressed, followed by plateauing suggested to indicate progressive irreversible injury.

Next, Razay et al[172] performed a prospective cohort study of 33 patients with probable iNPH of which 19 patients were operated but 10 declined surgery and 4 were re-examined while on the waiting list for shunt surgery. These **14** patients were included as a control group. Already 3-4 months after the baseline assessment, most patients in this control group showed worsening of symptoms: 9 patients on global ratings, 9 patients on gait and balance and 8 patients on dementia functioning. Of the shunted patients 89% improved in balance and gait and 67% in cognition.

In a prospective cohort study by Eide and Brean[174], patients underwent intracranial pressure monitoring, and patients with duration and level of wave amplitudes above specific cut-offs were selected for shunt surgery. Symptoms were graded pre- and 12 months post-operatively. All 24 patients with elevated amplitudes were offered shunt surgery, but **2** declined operation. At follow-up, those 2 patients showed marked clinical worsening. **Thirteen** of the other 14 patients with non-elevated amplitudes but similar in all other aspects, were not offered shunt surgery. The group worsened during the 12 months' follow-up. Another **12** patients assessed by the same two authors and similarly denied shunt surgery based on non-elevated intracranial pulse pressure amplitudes in another study, were reported "unchanged or worse" after 12 months.[175]

Savolainen et al[81] based the decision to shunt or not, on intracranial pressure monitoring with pre-defined cut-off values for continuous ICP and the presence of A- and B-waves. Twenty-five patients were shunted, and compared to **26** not shunted patients. In fact, after 3 months, a subset of untreated patients had improved spontaneously: 15% in gait and 11% in urinary or cognitive symptoms. After 5 years there were no longer any improved patients in the untreated group, instead 65% of the 17 still alive patients had a worsened walking ability, while 35% were unchanged. In the group of shunted patients, 47% still had improved gait compared to the preoperative assessment after 5 years, 33% were unchanged and 29% had worsened.

Pfisterer et al[173] monitored the continuous intraventricular pressure during 48 hours in their patients and shunted 55 patients who fulfilled specific criteria for the measurements. The other **37** were not operated. After a median of 7.2 years 15% of the untreated patients improved from gait disturbance, 60% were unchanged and 25% deteriorated. 55% deteriorated in mental symptoms, 9% were improved. For comparison 96% of shunted patients were improved in gait, 77% in mental and 76% in urinary symptoms after median 7.2 years.

Additionally, not included in the summary of number of untreated patients as no objective outcome measures were presented, in 1978 Hughes[177] et al retrospectively identified 12 iNPH patients where shunting had been strongly considered or recommended, but for various reasons not performed. After 7-36 months, the symptoms were improved in 1, unchanged in 5, and worse in 6 patients. Of the 27 shunted patients in that study, 17 could be postoperatively evaluated and 9 (33%) improved, 7 (26%) were unchanged and 11 (41%) deteriorated.

Moreover, Kahlon described the short-term outcome (mean 6.1 months) in patients not operated due to negative lumbar infusion tests and CSF tap tests.[178] These were 12 iNPH and 9 sNPH patients, but the results were only presented for the whole group of 21 patients. Of the 21 patients, 2 (10%) and 5 (24%) were improved in walking test seconds and time, respectively, the rest were reported as non-improved. In the same tests, of 54 treated iNPH and sNPH patients, 76% and 83% were improved, respectively. Four (19%) were subjectively improved without treatment, compared to 96% in the treated group of 54 patients.

Further, a negative correlation between the duration of the time lapse from diagnosis to operation, and outcome, was found in the study by Larsson et al on 74 NPH patients with different etiologies[92]. As published in 2019, Bådagård et al observed that waiting time was a negative predictor of outcome in iNPH[179].

1.5.2 Natural history of the preclinical phase

The natural course of the presumed preclinical phase, believed to include asymptomatic hydrocephalic ventricular enlargement, is only poorly described.

The size and shape of the ventricular system changes with increasing age: the ventricles become larger and the frontal horns are the first to widen, followed by the parieto-occipital and then the temporal horns. There is a sex difference in this progression: men's ventricles enlarge earlier than women's, and the mean size indexes including Evans' index in men are higher[180]. Tight medial and high convexity subarachnoid spaces are thought to be the first presenting features of DESH morphology[181].

Japanese researchers have described signs of hydrocephalic ventricular enlargement preceding development of NPH symptoms, and termed this "AVIM" for *asymptomatic ventriculomegaly with features of iNPH on MRI*. In

two population based prospective studies there were 790 individuals aged 60 years or 70-72 years in one[182], and 217 participants aged 70 years in the other[13]. One % presented MRI features but no symptoms, consistent with AVIM in these studies. During follow up of 8[182] or 10[13] years, 25-30% of those persons progressed to develop clinical symptoms of iNPH.
Metabolic disturbances have been shown already in the AVIM phase: the glucose consumption was lower in the cortical regions in patients with AVIM – while patients with clinical features of iNPH also had lower glucose metabolism in basal ganglia[183].

Similarly, as repeated clinical assessments were performed longitudinally in the population cohorts studied by Jaraj et al, they were able to observe that 45% of patients with asymptomatic ventricular enlargement or possible iNPH progressed in their symptoms as to fulfil the criteria for probable iNPH within follow up of median 11.5 years[184].

Although the pathogenesis is not well characterized, the chronic progressive nature of symptoms agree that the disease process likely begins several years prior to presentation. It is not understood why or when persons with this radiological finding develop coherent symptoms nor if all would develop hydrocephalic symptoms if they live long enough - or if compensatory mechanisms can in some instances be sufficient to avoid functional impairments.

1.5.3 Randomized controlled trials with delayed treatment

Further, performing RCTs to study the effectiveness of shunt treatment is another way of following the condition in an untreated phase. RCTs on shunting are scarce[156, 185]. The reason probably mainly being the same as declared above concerning studies on natural history: most researchers find it unethical to postpone surgery for study reasons.

However, there are at least three examples of RCTs on shunting in the literature. First, the double-blinded study on 14 patients with radiological and clinical diagnosis of iNPH but with negative CSF tap tests and infusion tests showing resistance to outflow not evidently elevated (R_o <12 mmHg /ml /min), and also fulfilling criteria for Binswanger's disease (subcortical arteriosclerotic encephalopathy) with extensive WMLs[110]. In the operation theatre the patients were randomized to open or ligated shunts. At the blinded three months' follow-up the 7 patients with open shunts had improved, while the 7 patients in the

placebo group had not changed. After opening of the ligated shunts, also those patients improved until the 6 months' follow-up.
At long-term follow-up after a mean of 42 months, three had died of causes unrelated to shunt surgery, and one was lost to follow up. Of the remaining ten patients, seven reported still being improved compared to before shunt surgery.

Second, the SINPHONI-2, an open-label trial on the effect of LP shunts[186], where 93 iNPH patients were randomized to immediate or 3 months delayed LP shunt surgery. Additional intervention by physiotherapy was adopted in both groups. Favourable improvement measured by ≥1 point on the mRS was seen only in 5% of those with delayed treatment after 3 months (2 of 42), compared to 65% in the immediate treatment group. In the postponed group 18% showed deterioration by one point or more on the mRS already after 3 months[152]. There were no differences in any adopted test for patients in the conservative arm on a group level, but significant improvements were seen in the immediate surgery group and in that group caregiver burden decreased significantly[186].

Third, Toma and Watkins reported in a letter to the editor of British Journal of Neurosurgery, of "a trial of a trial": an attempt to perform an RCT on shunting which was terminated due to recruitment difficulties[187]. The 14 patients included had been randomized to shunt surgery with shunts set to an opening pressure of 20 cmH2O ("closed") or to 5 cmH2O ("open"). Patients with "open" shunts improved their walking speed after 3 months, while patients with "closed" shunts did not. When those shunts were also set to 5cmH2O, their gait performance improved too and after one year the proportion of improved patients in the two groups were similar.

1.5.4 Summary

A total of **113** cases of objectively evaluated untreated iNPH patients were found in the literature and the majority deteriorated in their symptoms during follow-up of 3 months to 7 years, while only a handful of cases showed improvements. The designs of these studies result in class IV level of evidence according to CEBM (Centre for Evidence-Based Medicine) criteria. However, taken together, the homogeneity of the conclusions in the five cohort studies were assessed as providing relatively high ranking evidence that untreated patients deteriorate, and that the outcome is better in shunt treated patients – reaching level 2a according to CEBM level of evidence document[176].

In the three RCTs, altogether 56 patients were observed in conservative or placebo groups. After three months, all patients showed unchanged results on a group level, probably because the time interval was not sufficient to reveal deterioration in the control patients. Instead, the active treatment groups improved after that time.
Altogether, the knowledge about the natural course of iNPH is scarce, and the effects of postponed compared to early surgery, have not been studied.

1.6 Long-term outcome

Table 1A provides a compilation of available studies with at least 3 years follow-up of operated iNPH patients, and table 1B summarizes long-term studies where results are mixed with outcome before 3 years follow-up. These are considerably heterogenous in terms of e.g. inclusion criteria, outcome measures, statistical and reporting strategies, contributing to the large variations in the results.
The systematic review by Toma showed improved long-term outcome over the years[93], thought to be explained by improved diagnostics and safer neurosurgical and anaesthetic techniques, with a pooled improvement rate after 3 years of 73% in the newer studies.

Later deterioration in a subset of patients with initially good treatment effects have been described in many studies with repeated long-term follow-ups[168, 178, 188-193]. In the study by McGirt 9 of 99 patients declined after one year despite functioning shunts[168]. From the same centre, 55 patients were assessed yearly until 3-7 years after surgery: 25% of initially improved patients deteriorated in gait and cognition, and >50 % in urinary symptoms.[194]
Takeuchi presented long-term results from 482 iNPH patients with yearly follow-ups until 4 years after surgery[192]. At 3 months 93% of patients <80 years of age (n=400) and 82% of patients aged ≥80 (n=82) were improved. After 4 years the proportion of improved patients had sunk to 82% in the younger and 71% in the older group. All cases of non-sustained improvement were stated to be caused by other diseases or age-related changes. Simultaneously, in the Timed-up-and-go test, MMSE and mRS, deterioration of the mean score started at 3 years, and in urinary symptoms after 2 years. The tendency of decline was more pronounced in the older group. Noteworthily, in all parameters, in spite of this deterioration, the mean scores at 4 years were still better than the pre-operative results.

***Table 1A**: Studies on the long-term outcome in patients operated for iNPH, with at least 3 years follow-up. "N" is the number of operated iNPH patients included in each study, "% improved" is the reported proportion of improved patients in the long-term.*

Author	Year	N	% impr-oved	Long-term outcome measure	Follow-up, years	Comments
Greenberg[195]	1977	28	43	No/Moderate/Excellent overall improvement	3	12 of 28 patients still improved
Raftopolous [196]	1996	23	91	10m walk, various neuropsychological tests	5	91 patients improved until death or 5 years
Malm[197]	2000	42	26	Gait analysis, Barthel (ADL), MMSE	3	11 of 42 patients still improved (deceased included)
Mori[169]	2001	120	73	Japanese NPH grading scale	3	105 patients in long-term evaluation
Savolainen[81]	2002	25	47	Subjective assessment by letter or telephone	5	15 patients in long-term evaluation
Aygok[198]	2005	50	80	Clinical assessment of change in 3 domains	5	80% improved in dementia, 75% in gait
Tisell[199]	2006	38	64	Posted questionnaires	4	22 iNPH patients answered, 14 still improved
Kahlon[178]	2007	46	40	Clinical examinations or telephone follow-up	5	Results not presented separately for iNPH
Pfisterer[173]	2007	47	94	Clinical examinations	6	44 improved in gait, 3 declined later
Pujari[194]	2008	55	85	Clinical examinations	3-7	Only patients available at 3 years included
Mirzayan[200]	2010	51	91	Krauss improvement index	4-7	34 patients reached for long-term evaluation
Klassen[201]	2011	13	33	Klassen scale	3	Other neurologic disorders in 5 patients
Gölz[189]	2014	147	74	Kiefer scale	6	61 patients reached for long-term evaluation
Espay[188]	2017	30	33	Clinical impression	3	Revised diagnosis in 8 patients
Takeuchi[192]	2019	482	80	Japanese NPH grading scale	4	Only patients with 4 years follow-up included
Liu[191]	2020	58	57	Clinical tests + subjective	3	LP shunts. 57% subjectively improved.

***Table 1B**: Studies on the long-term outcome in patients operated for iNPH that included patients with less than 3 years' follow-up. "N" is the number of operated iNPH patients included in each study, "% improved" is the reported proportion of improved patients in the long-term.*

Author	Year	N	% impr-oved	Long-term outcome measure	Follow-up, months	Comments
Black[202]	1980	62	47	Stein and Langfitt scale	Mn 36.5	29 of 62 patients still improved
Vanneste[203]	1992	127	27	Clinical ordinal scales	Md 3.1	Slight improvement in 21, marked in 19 patients
McGirt[168]	2005	132	75	Clinical evaluation	Mn 18	99 of 132 patients improved
Spagnoli[170]	2006	66	60	Clinical assessment in 20, telephone in 45	Md 52	Improved with CVD: 52%, without CVD: 79%
Meier[204]	2006	63	67	Kiefer scale	Mn 34	51 patients in long-term evaluation
Illan-Gala[205]	2015	29	48	Klassen scale	Mn 37.8	14 of 29 patients still improved
Benveniste[190]	2018	69	-	Surgeons' clinical impression	Mn 44.4	Focused on deterioration

CVD, cerebrovascular disease

Retrospectively reviewing the charts of patients from 1999-2017, Gutowski found that 53 of 259 (20%) patients showed secondary deterioration[193]. Of these patients, 14 could again ameliorate, after shunt valve adjustments, diminishing the rate of secondary deterioration from 20 to 15%. Risk factors for secondary deterioration were higher age, newly diagnosed neurodegenerative diseases, and overdrainage requiring upregulation of the valve. The authors advocate thorough follow-up in the long-term to maximise long-term benefit and propose an algorithm for long-term optimization of shunt efficacy.
However, Benveniste found the effect of valve adjustments due to late deterioration, to last only shortly in the 6 patients where this was performed. Their study agreed that higher age was a risk factor for delayed progression, while classic symptom triad, adjuvant pre-operative testing, patients' sex, or time of follow-up was not of relevance[190].

In a Taiwanese retrospective long-term study that could reach 42 patients with lumboperitoneal shunts after 3 years, 80% were subjectively improved after one week to 3 months, and 57% after 3 years[191]. MMSE was improved from 18 to 25 in the short term but had again sunk to 18 points after 3 years. Indexes of improvement in five symptoms – mood, talking response, movement, attention, recalling memory - gradually declined, but without reaching the pre-operative level. They made the conclusion that the effect of LP shunts was not sustainable, but no comment was made about the expected course in untreated cases.

1.6.1 Factors predicting long-term outcome

1.6.1.1. Clinical presentation

Already in the early case series of patients treated during the years that followed the description of NPH in the 1960's, it was noted that patients with the complete triad of gait, cognitive and urinary disturbance or patients with predominantly gait disturbance were the most likely to improve by shunt surgery.[195, 202, 206, 207] This has been confirmed by later studies[92, 168], and the presentation of gait disturbance before dementia has been found to be beneficial[168, 208]. Further, many studies have shown that gait disturbance is the symptom that is the most likely to improve by shunting[76, 82, 192], also in a long-term perspective.[81, 168, 169, 197]
In other studies presence of the complete symptom triad had no predictive value on the long-term outcome[194, 205, 168, 203].

In the early studies, the observation that patients with only dementia or a more severe grading of dementia were less likely to improve, was made.[195, 202] In the Greenberg study from 1977, in a long-term perspective, patients with dementia who did initially improve, were found more likely to have only transient improvement than patients with predominant gait disturbance[195]. Greenberg speculated that these patients had concomitant AD, and in 1989 this notion was corroborated by Graff-Radford who suggested that when dementia predominates the clinical picture, concomitant AD should be suspected[76].
Several studies found that the cognitive symptoms, were least likely to improve by shunt surgery[81, 168, 205].
Conversely, the long-term study by Aygok in 2005 showed that 80% of NPH patients had an improved memory function in the short-term evaluation, and all of them had a sustained improvement after 3 years.
Koivisto followed up 147 initially well responding patients with regard to development of cognitive symptoms and found that 67 (46%) developed dementia in a follow-up of median 4.8 years. Eighteen of those patients had concomitant AD, 8 had vascular dementia, 22 had other possibly contributing factors but the remaining 8 (5%) were deemed to have developed iNPH-related dementia in spite of shunt treatment. Higher age at shunting, male sex, memory deficit preoperatively and memory deficit as leading symptom preoperatively were predisposing factors for this development. Interestingly Aβ or hyperphosphorylated tau findings in perioperative frontal cortical biopsies did not predict a later diagnosis of dementia.

Concerning the symptom duration at time of diagnosis, several studies have not been able to find any correlation to treatment effect in the short or long term. [178, 194, 66, 195, 202] However other studies showed a negative effect of longer symptom duration[92, 168, 208], although at least one of those studies showed good treatment effect in some patients with long symptom duration, emphasizing that the duration of symptoms should not be taken into consideration in the treatment decision.[92]
Further, a long duration of dementia has been associated with a less beneficial outcome.[76]

The patients' age at time of surgery was not found to be of consequence for the outcome in a short[92, 168, 195, 202], nor long-term perspective in many studies[168, 194, 195, 199,189]. Although in the study by Kahlon a larger proportion of patients below 75 years of age (64%) than aged 75 years or above (11%), continued to show improvement after 5 years[178]. Additionally, age as a predictive factor for the risk of delayed symptom progression has been found in several studies[190, 192, 205].

In many studies male patients are slightly over-represented, but the patients' sex has never been shown to be of relevance for the short- nor long-term outcome[168, 194].

1.6.1.2 Cerebrovascular comorbidity

One study from 2006 on 66 iNPH patients, evaluated if established cerebrovascular disease would have any effect on the long-term outcome in iNPH[170]. Cerebrovascular disease was defined as previous ischemic or haemorrhagic strokes, infarcts or moderate to severe hypodense white matter lesions on CT and was seen in 47/66 patients (71%). Several previous long-term studies excluded patients with previous strokes.[168, 169] Patients with cerebrovascular disease presented more pronounced symptoms pre- and postoperatively but their degree of improvement was similar as for patients without cerebrovascular disease in the short-term evaluation. Five patients (8%, all had signs of cerebrovascular disease at time of diagnosis) had strokes after 11 ± 8.4 months, but all had improved before they had strokes. In fact, their analysis showed that if patients who died (24%) or had strokes (8%) during the follow-up period were excluded, the results in the clinical outcome in short- and long-term were the same. This indicates a persisting good shunt effect of the hydrocephalic state *per se*. Altogether 79% of patients without and 52% with cerebrovascular disease had preserved improvement in the long-term follow-up at a mean of 52 ±24.8 months and the authors concluded that although patients with iNPH and cerebrovascular disease were a less favourable category of patients to treat, surgery should not be denied.
Further, the long-term outcome study by Kahlon in 2006 where 23 iNPH patients were followed up after a median of 5.5 ± 1.4 years showed similar incidence of cardiovascular and cerebrovascular disease in patients who continued to show improvement in the long-term, and those who did not[178].

1.6.1.3 Other concomitant diseases

Several studies have described that concomitant diseases hampered the long-term effects, in 38-100% of patients without sustained improvement this was said to be caused by a wide range of concomitant diseases that were known at time of surgery or emerging afterwards[178, 188, 190, 192, 201]. Examples from these studies include hip fractures, lower back pain, heart diseases, strokes, chronic

obstructive pulmonary disease, malignancies, Parkinson's disease, Progressive supranuclear palsy, Lewy-body dementia and AD.
Gölz et al[189] scored their patients in the Kiefer comorbidity index, CMI[209], where a list of diagnoses are assigned 1-3 points and the sum constitutes this index. They rated the long-term outcome in four levels: poor, satisfactory, good or excellent, finding a higher CMI in patients on the poor, than on the excellent outcome level.

1.6.1.4 Radiological findings and valve type

The importance of various radiological findings has been extensively studied in short-term studies but only rarely commented in a long-term perspective. There are a few published results on radiological markers' relation to long-term improvement: McGirt saw more favourable long-term outcome in patients presenting with corpus callosum impingement, while cerebral atrophy and WMLs were not of significance in that study[168]. Neither could Pfisterer relate periventricular lesions or Evans' index to long-term outcome[173].
Type of valve was not significantly associated with outcome 3 years after surgery[194].

1.6.1.5 Hydrodynamic and CSF drainage tests

Several of the early long-term study authors argue, based on comparison with other studies, that their diagnostic approaches with invasive supplementary tests is predictive of beneficial long-term outcomes: different methods of ICP monitoring[81, 170, 173], ELD or resistance testing[198], ICP monitoring and ELD[168]. However, as stated by both McGirt et al[168] and Pfisterer et al[173], conclusions about these tests' predictive value can hardly be made, when only reporting outcomes from one trial arm.

1.6.2 Summary

A long-term outcome of more than 70% of patients improved after 3 years or more is found in many studies.
Of factors influencing the long-term outcome, there appears to be a consensus regarding that a clinical picture dominated by gait disturbance is consistent with better long-term outcome. Patients with established cerebrovascular disease

benefit from treatment in a long-term perspective, but to a lesser extent than patients without cerebrovascular disease, due to the risk of ischemic events. Also, other comorbidities may hamper the long-term effects, and it is important to assess these at time of diagnosis.
Not surprisingly, higher age at time of surgery was shown to influence the long-term outcome in some patients, but noteworthily, sustained improvement to some degree was shown in up to 71% of patients aged 80+ in the long-term.

No previous study has described the long-term outcome in a national quality registry setting, with prospective and extensive data collection as part of routine care.

1.7 Survival and causes of death

Survival in treated iNPH patients has been shown to be diminished compared to the general population. The study by Malm et al calculated the relative risk of death at 3 years after surgery to 3.3 compared with healthy elderly controls[197], and Tisell et al showed a Standardized mortality ratio (SMR: observed/expected deaths) of 2.52, 95% CI 1.3-4.4[199]. Both found the survival curves of iNPH patients to be similar to those of first-ever stroke sufferers.
Kahlon et al found an annual death rate of 7.4% compared to 3.2% in the general population of the same age range[178].
Pyykkö et al instead compared 283 patients treated for iNPH to a cohort of 253 patients investigated for, but not diagnosed with, iNPH. The survival was better in those with iNPH: HR 0.63, 95% CI: 0.5-0.78, $p<0.001$[11].

Savolainen could not find any difference in survival between shunted iNPH vs patients not believed to suffer from iNPH, hence not shunted patients: 32 vs 35% patients had died after 5 years[81].

However, in the population study by Jaraj, including 1235 persons prospectively followed longitudinally with clinical examinations and CT of the brain[184] mortality in 24 untreated persons with presumed probable iNPH was significantly increased, by an adjusted HR of 3.8, 95% CI 2.4-5.8 (p not stated).

1.7.1 Factors influencing survival

The above cited study by Pyykkö of 283 iNPH patients, published in 2018[11], found a poorer survival in those with chronic heart failure or diabetes type 2. Coronary heart disease, atrial fibrillation, other arrythmias or arterial hypertension were not shown to influence survival in this cohort, nor was the patients' sex.
The presence of AD pathology - Aβ and/or hyperphosphorylated tau - in frontal cortical biopsies from these patients was not shown to influence survival.
Another study from the same research group, published in 2012[34], reported the influence on survival of AD pathology in frontal cortical biopsies taken from 468 patients evaluated for iNPH, assumedly included also in the 2018 study. Neither in that study were the findings in frontal cortical biopsies shown to influence survival[34].

1.7.2 Causes of death

Many studies listed the causes of death in their samples, and several authors noted that deaths due to specifically cerebrovascular disease or in general cardiovascular disease were common (32-66%) [81, 170, 178, 196, 197, 199, 200].
In at least one study, malignant disease was an exclusion criterion[81]. Mirzayan did not apply this criterion, but observed that death due to malignant disease in their sample of treated iNPH patients was unexpectedly low, only two of 29 deaths[200].
None of these studies compared the causes of death to a control group.

1.7.3 Summary

The mortality in treated iNPH patients has been shown to be two to three times increased compared to the general population and in untreated persons almost four times increased. Chronic heart failure and diabetes were risk factors for earlier death in iNPH patients.
Death due to cerebrovascular disease or other cardiovascular diseases were common, and malignancies were felt to be under-represented.

Survival in iNPH has not been studied and compared to the general population in any large registry studies and the patients' causes of death have never been compared to the general population.

2. Aims

The aims of this thesis were to study the natural course in untreated iNPH patients, and the effect of postponed treatment, with regard to outcome and survival. Moreover, the aim was to study the long-term outcome and survival in a large unselected cohort of treated iNPH patients from all over Sweden, registered in the Swedish Hydrocephalus Quality Registry, SHQR.

The specific aims for each paper, were:

I To describe if, how much, and in what symptom domains patients with iNPH change during a waiting time of 6-24 months. The aim was also to compare the postoperative results of waiting patients with iNPH patients who had shunt surgery performed within 3 months from diagnosis.

II To study the effect of delayed compared to early shunt surgery on survival in iNPH. To study if causes of death differ between patients with delayed or early surgery.

III To describe the long-term outcome of iNPH patients included in the SHQR, the incidence and influence of reoperation due to complications, and the influence of vascular risk factors and vascular comorbidity on outcome.

IV To study survival and causes of death in a large unselected cohort of treated iNPH patients from the SHQR, and how vascular risk factors and vascular comorbidities, preoperative symptom severity, and response to shunt surgery influence survival.

3. Patients and Methods

***Table 2**: Overview of patients and variables in paper I-IV.*

	Paper I	Paper II	Paper III	Paper IV
iNPH patients, n	102 (33+69)		979	
Inclusion years	2004-2012		2004-2011	
Catchment area	Sahlgrenska University Hospital (mainly VGR region)		Sweden: National registry, SHQR	
Control group, n				4890
Symptom gradings				
iNPH scale	X	X		
Gait, balance, continence scales			X	X
Modified Rankin Scale	X	X	X	X
Mini-mental state examination (MMSE)	X	X		X
Vascular risk factors and comorbidities				
Hypertension	X	X	X	X
Diabetes	X	X	X	X
Cardiovascular disease	X	X		
Heart disease			X	X
Stroke			X	X
Claudication				X
Type of data included				
Long-term follow-up letters			X	
Complications		X	X	
Dates and causes of death		X		X

3.1 Papers I and II – natural course study with long-term follow up

Papers I and II study the same 102 patients who were all diagnosed with iNPH and scheduled for shunt surgery at Sahlgrenska university hospital in Gothenburg between 2004 and 2012. The catchment area for investigations regarding NPH was from the whole region of Västra Götaland (VGR), constituting approximately 1.6 million inhabitants, plus the northern part of Halland county.

All underwent the same routine diagnostic procedure with brain MRI, or CT if MRI was contraindicated, and thorough clinical examinations by a physician, a physiotherapist and a neuropsychologist. Lumbar puncture and ancillary tests such as infusion test[126], CSF tap test[131] or radionuclide cisternography were performed when considered clinically indicated.

After the clinical evaluations, all patients were presented at a multidisciplinary conference attended by one or more consultant neurologists and neurosurgeons from the Hydrocephalus team. At this conference the final diagnosis and decision to refer the patient for shunt surgery were made. The diagnosis of iNPH was made in accordance with the international iNPH guidelines.[3] The date of decision to refer for shunt surgery constitutes the baseline date for both papers, and that timepoint is termed "Preop 1" in paper 1.

Symptom severity was measured by the iNPH scale[150], which is a validated continuous, norm-based scale covering the four symptom domains of gait, balance, cognition and continence. Each domain is assessed by different tests and ratings as illustrated by figure 5. The results convert into separate scores, 0-100, for each domain. A total iNPH scale score, also 0-100, is then calculated with the gait domain given double weight, as shown in the figure. In each domain, the score 100 represents a normal performance of healthy elderly individuals. Additionally, patients were tested by the Mini-mental State Examination, MMSE[210] and their level of functional independence or disability was rated with the modified Rankin Scale, mRS[148] (described in chapter 3.2).

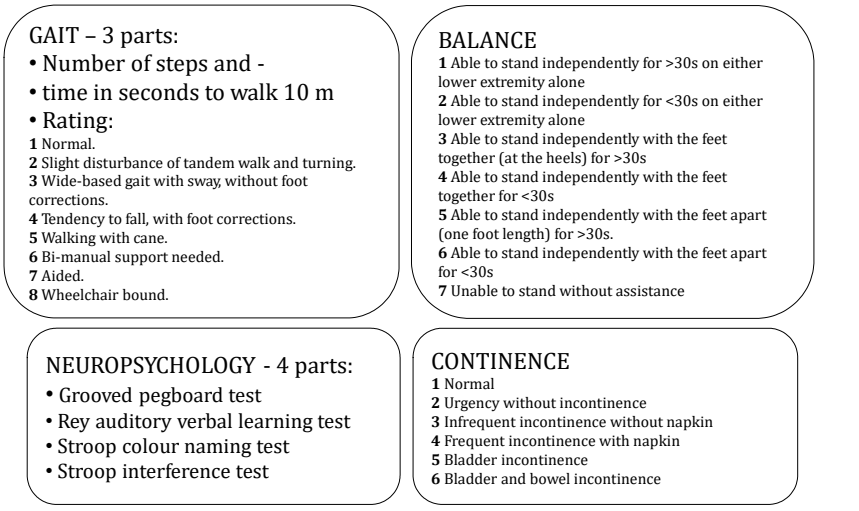

Figure 5: *iNPH scale. Tests used in the four domains of the iNPH scale, and the equation used for calculation of the total score.*

The 102 patients comprise two groups, defined by their waiting time for surgery. In 2010-2011 when the study was initiated, the situation at the Sahlgrenska university hospital was deeply problematic with unacceptable waiting times for elective neurosurgical procedures. Additional financial support was provided in 2011 to shorten the queues for surgery. Between the 5th of March and 31st of December 2011 all patients who had been on the waiting list for more than six months when scheduled for shunt surgery, were included in the study group termed $iNPH_{Delayed}$, n=33. These patients had a second clinical assessment by a physician, a physiotherapist and a neuropsychologist just before their surgery, in order to document a new baseline level for comparison with post-operative results and enabling to study the course of symptoms during the wait: "Preop 2".

The other 69 patients were included as a contrasting group, defined as all iNPH patients prospectively included in the local hydrocephalus database diagnosed and operated in 2004-2012 who had waited maximum 3 months for their surgery:

$iNPH_{Early}$. Baseline data for these two groups are presented in table 3. The post-operative assessment was made 3 months after surgery with the same symptom gradings as pre-operatively and by the same routine in all patients.

Table 3: *Baseline data in papers I and II.*

	$iNPH_{Delayed}$ (n=33)	**$iNPH_{Early}$ (n=69)**	***p***
Age, years, median (range)	76 (55-89)	70 (48-84)	0.006
Sex (F/M), n (%)	16/17 (48/52)	32/37 (46/54)	1.0
MMSE, median (range)	25 (14-30)	25 (9-30)	0.42
Modified Rankin Scale, median (range)	2 (1-4)	2 (1-4)	0.50
iNPH scale scores, median (range)			
Total score	45 (7-94)	49 (2-95)	0.16
Gait score	23 (0-95)	39 (0-100)	0.15
Neuropsychology score	40 (5-100)	49 (3-100)	0.45
Balance score	67 (0-100)	67 (0-100)	0.08
Continence score	60 (20-100)	60 (0-100)	0.82
Duration of symptoms, months, median (range)	24 (8-132)	24 (6-360)	0.70
Cerebrovascular risk factors, n (%)			
Hypertension	20 (61)	24 (35)	0.019
Cardiovascular disease	10 (30)	12 (17)	0.20
Diabetes	4 (12)	10 (14)	1.0
Time before surgery, months, median (range)	13.2 (6.8-23.8)	0.2 (0.1-2.7)	<0.001

The waiting time from referral for shunt surgery, to being scheduled for shunt surgery, was median 13.2 months for $iNPH_{Delayed,}$ In the contrast group, $iNPH_{Early,}$ the waiting time was median 0.2 months. Patients in $iNPH_{Delayed}$ were older, with a median of 76 years, compared to median 70 in $iNPH_{Early}$. A little more than

half were male in both groups. There were no significant differences in any of the symptom grading scales. Nor was there any difference in the duration of symptoms at time of diagnosis. The frequency of vascular risk factors or comorbidities was the same for diabetes and cardiovascular disease, but hypertension was more common in $iNPH_{Delayed}$..

All but one patient underwent shunt surgery. One patient in $iNPH_{Delayed}$ that was admitted to the neurosurgical ward for shunt surgery after a waiting time of 14 months, fell ill with an infection that caused surgery to be again postponed and then succumbed before surgery was performed. That patient was included in the study, as the inclusion criteria of having waited more than 6 months from the date of decision of surgery until being scheduled for surgery were fulfilled, and the patient had undergone the second pre-operative investigation. Another four patients died before the postoperative examination had taken place, after two, four, five and eight months. One patient refused to do the post-operative follow-up.
In $iNPH_{Early}$ four patients were not postoperatively assessed, one because of death 5 months after shunt surgery (acute myocardial infarction) and three were lost to follow-up. One of those three was thought to be deceased at the time when paper I was written. However, the CDR data later commissioned for paper II clarified that this had been a misconception: the patient lived another 4.5 years after shunt surgery.
Consequently, postoperative assessments were available for 27 patients in $iNPH_{Delayed}$ and for 65 patients in $iNPH_{Early}$.

For paper II data was commissioned from the National Board of Health and Welfare's Cause of Death Registry (CDR) on all patients who were deceased before the 16th of June 2016: their dates and causes of death.
The type and number of complications were collected from medical files. They were categorized into 1. Major - complications requiring additional surgery or caused significant disability: larger subdural hematomas, obstruction or infection of the shunt catheter, stroke, intracerebral hemorrhage, or postoperative epilepsy and 2. Minor - complications that did not cause significant disability and did not require additional surgeries: postural headaches, smaller subdural effusions or hygromas, which resolved after adjustment of the shunt valve.
Causes of death were categorized into groups based on ICD-10 diagnostic code chapters.

In paper I the primary outcome measure was the iNPH scale, and in paper II it was mortality.

3.2 Papers III and IV – registry studies on long-term outcome and survival

The Swedish Hydrocephalus Quality Registry, SHQR, was founded in 2004, and all adult patients operated for hydrocephalus, including iNPH, are registered. Data for all patients with the diagnosis of iNPH who had been operated and registered in the SHQR during 2004-2011 were extracted on the 1st of September 2014. These 979 iNPH patients were included in both papers III and IV.

During those years, five of the six neurosurgical centers in Sweden reported all patient data to the SHQR. Only the county of Stockholm did not participate, meaning that the coverage was about 80% of the Swedish population[17]. The board of SHQR effectuated quality controls in the different centers regularly, to monitor the coverage and quality of data. These were performed by external review by representatives from another centre, who compared registry data to data in medical files and patient administrative systems in a standardized manner.

Symptom severity pre- and 3 months' postoperatively were graded using the same ordinal scales for gait, balance and continence, as used in the iNPH scale[150] (figure 5). The only difference was that the continence scale has one extra grade, for indwelling urinary catheter, which was coded as score 7 in this study. Cognition was assessed by the MMSE[210]. General disability or need for help was recorded by the modified Rankin Scale[148]. Further, presence or absence of vascular risk factors in form of diabetes mellitus and hypertension, and comorbidity of stroke or heart disease were registered. Presence or absence of peripheral arterial vascular disease, claudication, was added later to the registry and this variable was only included in paper IV. Baseline data for papers III and IV are presented in table 4 and a method overview is shown in figure 6.

Of the 979 patients 974 primarily had received shunts, but five had been operated with endoscopic third ventriculostomies. Three of those five were re-operated with shunts, after two weeks, six weeks and eight months, respectively. Short-term outcome data for principally the same group of patients, were previously reported by Sundström et al[211].

Table 4: *Baseline data in papers III and IV.*

	iNPH patients, n=979
Demography	
Age (years), median (IQR)	74 (68-78)
Sex, female, n (%)	413 (42)
Symptom grading scales	Median (IQR)
Gait scale (n=835)	4 (3-6)
Balance scale (n=747)	3 (3-5)
Continence scale (n=814)	3 (2-4)
MMSE (n=737)	25 (20-28)
mRS (n=755)	2 (2-3)
Vascular comorbidity	n (%)
Hypertension (n=891)	438 (49)
Diabetes Mellitus (n=887)	189 (21)
History of stroke (n=874)	119 (14)
Heart disease (n=892)	231 (26)
Claudication (n=458)	7 (1.5)
Number of vascular comorbidities	n (%)
0	372 (38)
1	316 (32)
2	205 (21)
3	74 (7.6)
4	9 (0.9)
5	0
None reported	3 (0.3)
Number of comorbidities, median (IQR)	1 (0-2)

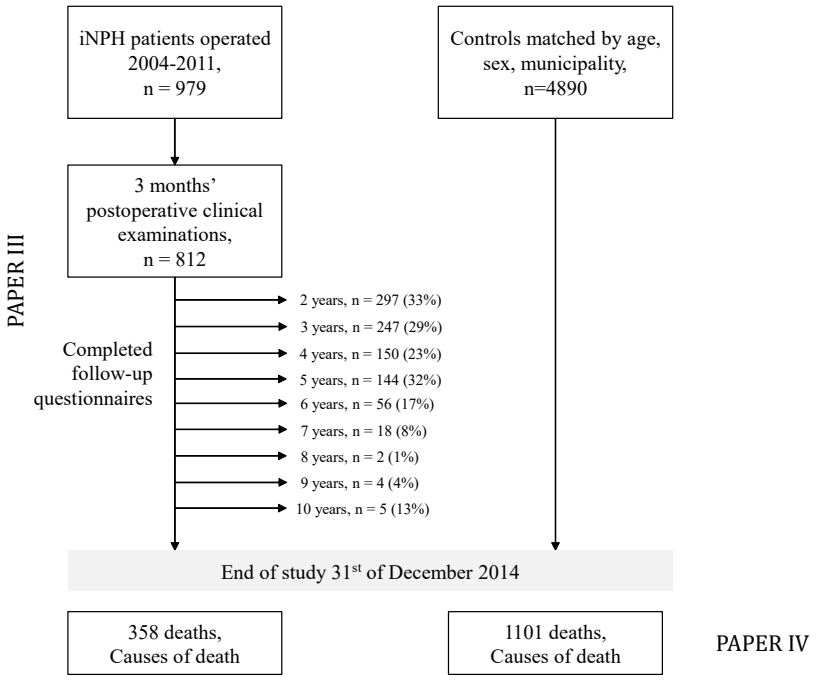

Figure 6: *Overview of patients and methods in paper III and IV. Percentages within parentheses represent proportions of replying patients for each year of available patients (alive patients with follow-up within that time range).*
The median follow-up time was 5.9 (IQR 4.2–8.1) years.

Date and type of complications and revision surgeries, which are also continuously reported to the SHQR, were also extracted. Only those complications that led to different kinds of new surgeries were analyzed in this study.

The SHQR registers separate categories for 15 different causes of renewed surgery and 10 surgical interventions. These were categorized into four groups: 1) Mechanical, most commonly shunt obstruction or displacement; 2) Infections, intraabdominal, skin or CNS infections; 3) Subdural hematomas, evacuation of hematoma and/or ligation of shunt; 4) other or not specified cause of renewed surgery.

The long-term follow-ups in the SHQR are made by posted questionnaires, accompanied by a cover letter explaining the purpose and asking for the letter to be replied by the patient, a next-of-kin or caretaker. See *appendix 1* for a translated version of this questionnaire. Register secretaries at each center were instructed initially to send out these questionnaires annually, starting two years

after surgery. However, in 2010 this approach was changed to follow-ups after 2, 5 and 10 years. In this study all available filled out questionnaires were grouped by number of years from surgery, as shown in figure 6. Two letters had to be excluded from this study, as the questionnaire had been returned by the same two patients twice during one year.

The long-term outcome measures in paper III were:

1. Patients' assessment of general health compared to before surgery – better, unchanged or worse (the question asked in the questionnaires was *"How are you feeling now, compared with your condition before surgery?"*)
2. Crude self-assessed modified Rankin Scale, smRS, ratings (Table 5).
3. smRS ratings compared to preoperative mRS.

For paper IV, a control group from the general population was selected by Statistics Sweden. Five controls per patient were matched by their age at year of surgery, sex, and habitational municipality. Only for one patient it was not possible to find matching controls and the resulting number of control persons is 4890.
For both patients and controls, dates and causes of death until the 31st of December were commissioned from the Cause of Death Registry, governed by the National Board of Health and Welfare. Until that date, 358 (37%) patients and 1101 controls (23%) had died.

The primary outcome measure in paper IV was mortality.

Table 5: *mRS*[148] *and smRS scales, the latter translated from Swedish. The mRS was used in clinical evaluations pre- and postoperatively in papers 1-IV. The smRS was used for patient's self-assessment of their degree of independent daily function or disabilities in the long-term evaluations, paper III.*

	Modified Rankin Scale, mRS	**Self-assessed modified Rankin Scale, smRS (paper III)** *Headline in the questionnaire: "Disability/need for assistance"*
0	No symptoms at all	No problems
1	No significant disability despite symptoms: able to carry out all usual duties and activities	Some problems that do not restrict my lifestyle
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance	Minor disability, some restrictions to my lifestyle, no need for assistance
3	Moderate disability: requiring some help, but able to walk without assistance	Some disability, which clearly restricts my lifestyle, need for assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance	Severe disability, dependent but not in constant need of assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention	Very severe disability, in need of constant care, day and night

3.3 Statistics

For comparison of categorical or continuous variables between two groups, the Mann-Whitney U test (I-IV) and for within-group comparisons the Wilcoxon signed ranks test was used (I-IV). For comparisons between more than two groups, the Kruskal-Wallis test was used (IV)
Proportions were compared using Chi-2 or Fisher's exact test (I, IV) or only Fisher's exact test (II-III).
Correlations were tested by Spearman rank correlation (I, III)
To analyze the influence of the vascular comorbidities in paper III, odds ratios with a 95% confidence interval were calculated by logistic regression analysis adjusted for age and sex.

Survival analyses (II, IV) were performed by the Kaplan-Meier method, and between-group comparisons were made with the Log-rank test. Further, survival analyses were performed by univariable and multivariable Cox proportional hazards models. In multivariable models, a forward stepwise approach was applied, with rejection of variables not reaching below the 0.05 significance level. The proportional hazards assumption was assessed by goodness-of-fit tests and visual analysis of scaled Schoenfeld residuals against time.
Ordinal grading scales (gait, balance, contincence, mRS) were dichotomized at the median before entry into Cox models, while age, MMSE and the iNPH scale were used as continuous variables.

The median follow-up in the two survival studies (II, IV) was calculated by the reverse Kaplan-Meier method[212].

All significance tests were two tailed and the statistical significance was set at the 0.05 level, without corrections for multiple testing.

Analyses were performed with SPSS version 20.0 (I) and 24.0 (II-IV), Stata version 14.0 IC (II, IV) and R version 3.2.219 (II).

3.4 Ethics

In all studies the data were collected as part of routine, on clinical indications, and no additional investigations or treatments were added. Patients or their next-of-kin were informed and consented of data collection for study purposes.

The natural course study (papers I and II) was approved by the Regional Ethical Review Board in Gothenburg, Registration number 009-13.
The long-term study (papers III and IV) was also approved by the Regional Ethical Review Board in Gothenburg, Registration number 492-14, with addition T006-15.

4. Results

4.1 Paper I

4.1.1 Symptom development during 6-24 months' wait in $iNPH_{Delayed}$ – the natural course

During the wait for surgery, $iNPH_{Delayed}$ deteriorated in the total iNPH score from median 45 to 37. There was a significant decline in mRS, MMSE and in all domain subscores of the iNPH scale, except for the continence domain score where the decline was at trend level.
There was a large range of the magnitude of change in individual patients, with iNPH score changing by -47 to +7. None of the baseline variables was shown to correlate or associate with the magnitude of change: sex, comorbidities, waiting time or symptom burden at baseline.
The proportion of patients able to live independently, defined as mRS ≤2, was 55% initially, but 39% at preop 2, $p<0.001$. None had an mRS of 5 at Pre-op 1, but 5 (15%) were assigned this score at Pre-op 2, which signifies being severely disabled.
Four patients (12%) had improved by at least 5 points on the iNPH scale during the wait, 11 were unchanged (33%) and the remaining 18 patients had deteriorated by at least 5 points (55%).

4.1.2 Effect of delayed compared to early shunt surgery in iNPH

Although patients in both groups improved to the same extent after shunt surgery, patients in $iNPH_{Delayed}$ had a less beneficial outcome in the post-operative examination. As their symptoms had increased while waiting, a surgical effect of the same magnitude as for $iNPH_{Early}$ was not sufficient to render the final result after surgery significantly better than results at the Pre-op 1 investigation, at the time of diagnosis (figure 7). This pattern was seen in the total iNPH score, the MMSE and the mRS.

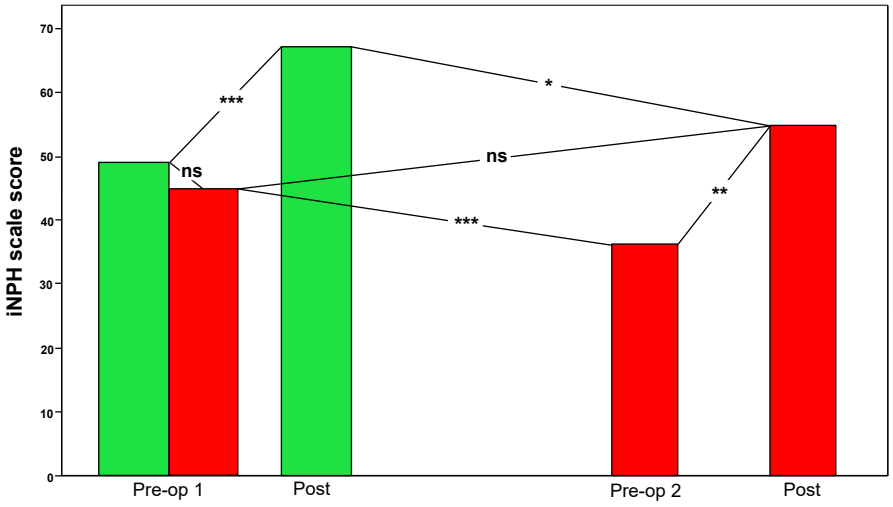

***Figure 7**: Development in total iNPH scale score for iNPH patients with 6-24 months delayed shunt surgery, $iNPH_{Delayed}$ (red bars), and iNPH patients with surgery within 3 months from diagnosis, $iNPH_{Early}$ (green bars).*
p<0.05, **p<0.01, *<0.001; ns, not significant*
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Of the domain subscores of the iNPH scale, all four improved after surgery in $iNPH_{Early}$.
Regarding the specific domain scores, in $iNPH_{Delayed}$ improvements were seen in gait and balance compared to the preoperative results directly before surgery (Pre-op 2), but no significant change was seen in the neuropsychology or continence scores after surgery.
The development in the iNPH scale for all individuals is visualized in figure 8.

In the statistical analyses in paper I, no age-adjusted method was used. To perform an adjusted analysis, an explorative logistic regression analysis was added. The outcome (dependent) variable was improvement post-operatively by at least five points on the iNPH scale, or not. Covariates reaching $p<0.1$ in univariable analyses were included in a stepwise forward approach into a multivariable model (Table 6). In this post-hoc analysis, the waiting time from

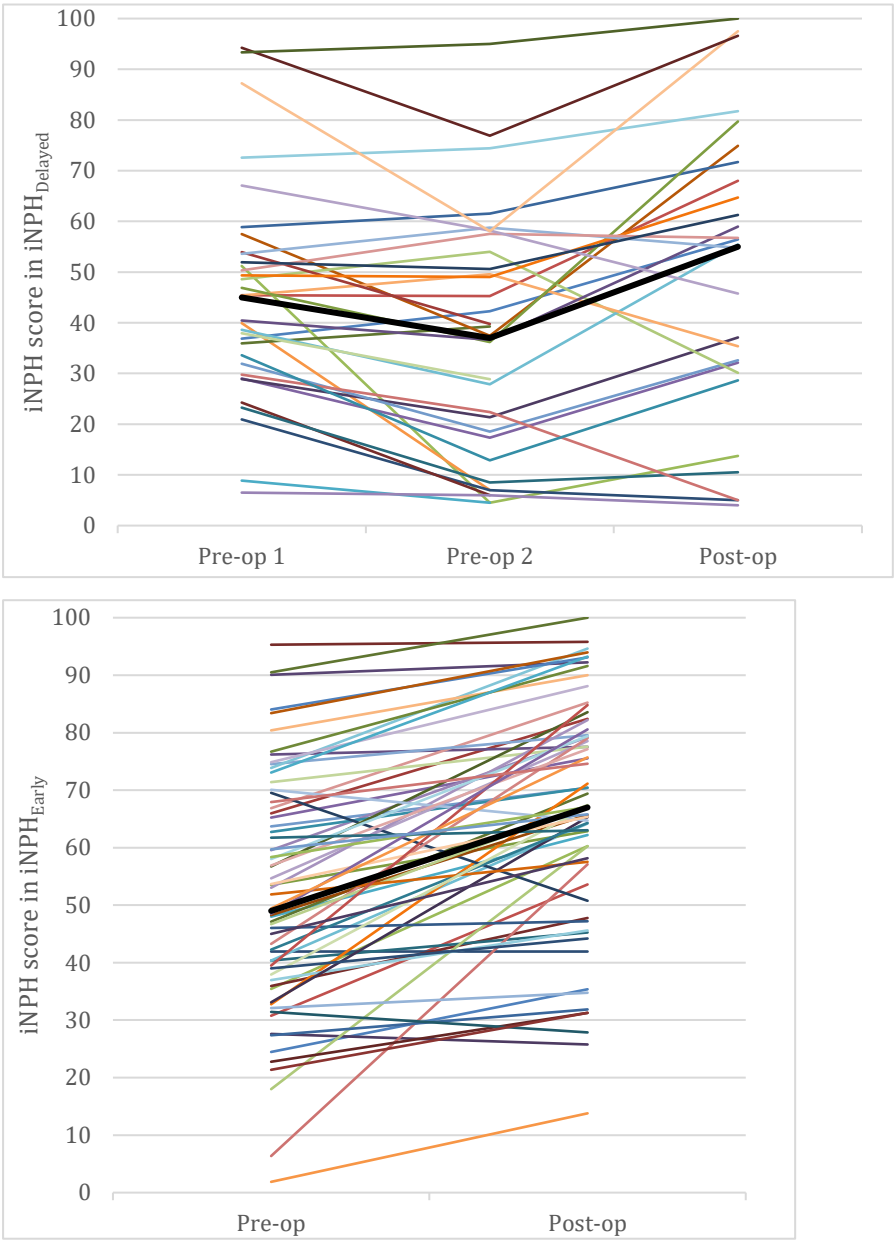


Figure 8: *Development in the iNPH scale. The upper plot shows pre-operative examination at time of diagnosis (Pre-op 1), after median 13 months wait for surgery (Pre-op 2), and 3 months post-operatively (Post-op) in* $iNPH_{Delayed}$*. The lower plot shows pre- and 3 months postoperative examinations in* $iNPH_{Early}$*. In both figures, the bold black lines represent the median results.*

date of diagnosis to surgery, increases the odds of not being improved postoperatively by 9% per one extra month's wait. Age at time of diagnosis was of no importance for being improved post-operatively or not. Consequently, this analysis supports the conclusion of unnecessary waiting time causing less beneficial outcome. Further, hypertension was more common in the delayed group, and cardiovascular disease was at trend level more common. However, none of these factors were shown to influence the odds of being improved (Table 6).

Table 6: *Logistic regression model of baseline variables' and the waiting time's influence on outcome in the 92 post-operatively assessed iNPH patients. The outcome variable was defined as improvement by ≥5 points on the iNPH scale, or not.*

	Univariable analysis			**Multivariable analysis**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Demography						
Age (years)	1.05	0.995 - 1.11	0.078	0.999	0.935 - 1.07	0.98
Sex (M)	1.99	0.784 - 5.03	0.15			
MMSE	0.926	0.833 - 1.03	0.15			
Modified Rankin Scale	2.24	1.29 - 3.90	0.004	2.18	1.14 - 4.19	0.019
iNPH scale scores						
Total score	0.990	0.968 - 1.01	0.38			
Gait score	0.997	0.981 - 1.01	0.73			
Neuropsychology score	0.987	0.969 - 1.01	0.14			
Balance score	0.990	0.972 - 1.01	0.28			
Continence score	0.996	0.997 - 1.02	0.72			
Duration of symptoms (months)	0.995	0.983 - 1.01	0.47			
Comorbidities						
Hypertension	1.37	0.547 - 3.44	0.50			
Cardiovascular disease	2.72	0.722 - 10.2	0.14			
Diabetes	1.48	0.445 - 4.93	0.52			
Time before surgery (months)	1.09	1.02 - 1.17	0.017	1.09	1.01 - 1.18	0.029

4.2 Paper II

The 102 patients were followed up with regard to survival on the 17th of June 2016. Until then, 17 (52%) patients in $iNPH_{Delayed}$ and 16 (23%) patients in $iNPH_{Early}$ had died, p=0.006. The crude 4-year mortality was 39.4% compared to 10.1% (p=0.001). The median follow-up was 7.3 years in total; shorter in $iNPH_{Delayed}$ than in $iNPH_{Early}$ (5.4 vs 7.4 years, p<0.001). The proportion of complications was similar in the two groups.

Cox regression modelling was used to investigate the influence of the baseline variables on survival. Study group, age, MMSE and the total iNPH scale score were each found to be significant in univariable analyses. In the multivariable model, only age and whether patients were in the delayed or early groups, were significant. Patients in $iNPH_{Delayed}$ had a HR of 2.57; 95% CI 1.13-5.83, p=0.024.

A Kaplan-Meier plot is shown in figure 9. Before plotting of these curves, adjustment for the age difference between the groups was performed in the following way: patients older than 84 years in $iNPH_{Delayed}$ and patients younger than 55 years in $iNPH_{Early}$ were excluded, creating groups with the same age range of 55-84 years, median 72 vs 71, p=0.18.

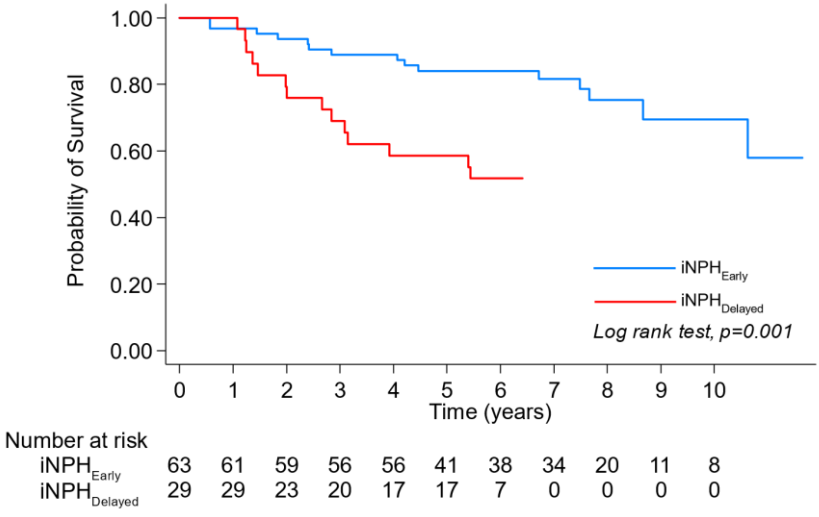


Figure 9: *Age-adjusted Kaplan-Meier plot of survival in the two groups.*

Death due to malignant diseases was more common in $iNPH_{Early}$: 4 of the 16 patients had this cause of death, compared to 0 of 17 in $iNPH_{Delayed}$. In the other seven categories of causes of death (Pneumonia, Dementia, Neurologic disease, Hydrocephalus, Cardiovascular disease, Cerebrovascular disease, Fall accidents) there were no significant differences. None of the deaths were related to shunt surgery.

4.3 Paper III

4.3.1 Long-term outcome

The proportion of patients responding that their health condition was better, unchanged or worse 2-6 years after surgery is shown in figure 10, along with the physican's assessment at 3 months.

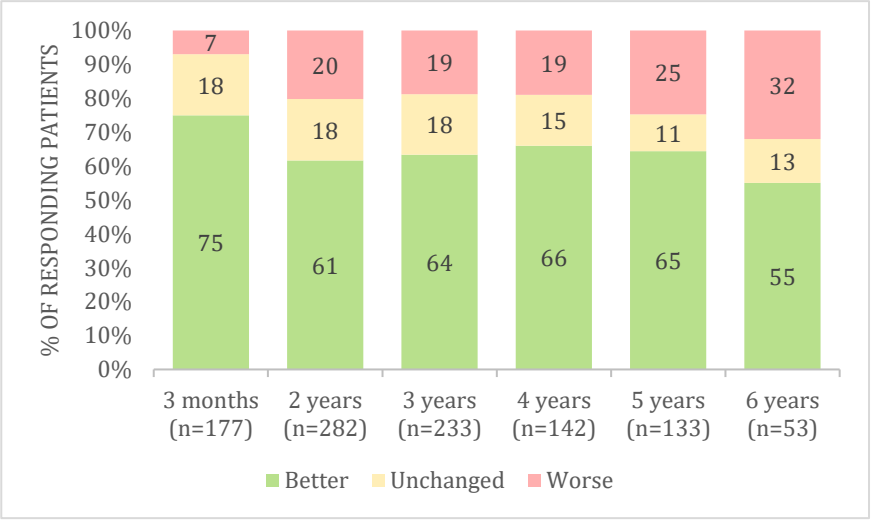


***Figure 10**: Postoperative health condition compared to before surgery in 979 iNPH patients, the numbers are % of patients. The 3-months evaluation was carried out in the clinical follow-up setting and this variable was included later in the SHQR, hence only registered for 177 patients. Results at the 2- to 6-year evaluation come from follow-up questionnaires, where the question asked was "How are you feeling now, compared with your condition before surgery?" n: number of patients responding to this question at each time point.*

Comparing the pre-operative mRS to the self-reported mRS (smRS) used in the questionnaires, there was a significant improvement on a group level after 2 years, but not in the questionnaires returned at 3, 4, 5 or 6 years after surgery. However, the proportions of improved patients were similar at the 3 months' clinical examination, where 39% had an improved mRS: 41, 41, 38, 40 and 40% had improved in their smRS compared to the pre-operative mRS after 2, 3, 4, 5 and 6 years, respectively.

4.3.2 Influence of vascular comorbidity

Patients with or without each of the reported comorbidities replied similarly to how their general health condition was compared to before surgery, in the 2 to 6-year groups.

The magnitude of change in the mRS to smRS after 2 to 5 years, was the same for patients with or without the different comorbidities on a group level. However, after 6 years patients with earlier strokes or with hypertension showed a smaller improvement than patients without these factors.

There were no significant correlations between the number of comorbidities and the development in mRS to smRS scores, nor with the evaluation of health condition.

4.3.3 Influence of complications leading to re-operations

Reoperations due to complications were performed in 26% of the patients, 58% of those operations took place during the first year after surgery. The median number of reoperations that those patients were subjected to was 1, and the range was 1-5. Of the whole cohort of 979 patients, 14% had re-operations due to mechanical complications, 6.4% due to infections, 3.7% due to subdural hematomas and 9.1% due to other or not specified causes. These groups are partly overlapping.

Analyzing the long-term outcome questionnaires returned from patients who had, or had not, been subject to re-operations, there were no significant differences in any of the outcome measures after 2-6 years.

4.3.4 Additional findings

Patients aged 80 or above at time of surgery indicated to the same extent as patients below 80 years of age, that their general health was still improved after 2, 4, and 5 years, compared to before surgery (Table 7). Only in the group of patients who returned questionnaires after 3 years, there were more patients below 80 that reported feeling improved. After 6 years the proportions were also similar but there were only 2 replies from patients in the higher age group.

Table 7: *Patients assessed as improved at the 3 months follow-up, and patients reporting themselves still improved after 2-5 years, per age category.*

	<80 years	**≥80 years**	**p**
3 months	77% (118/153)	58% (14/24)	0.075
2 years	62% (144/234)	60% (29/48)	0.87
3 years	66% (138/208)	40% (10/25)	0.014
4 years	68% (86/126)	50% (8/16)	0.17
5 years	65% (77/119)	64% (9/14)	1.0

4.4 Paper IV

The median follow-up time was 5.9 years, IQR 4.2-8.1. The estimated 5-year survival for iNPH patients was 69%, and 82% for controls and the HR for iNPH patients was 1.81, 95% CI: 1.61-2.04, p<0.001.

4.4.1 Influence of symptom severity, vascular comorbidities and post-surgical results on survival

Baseline symptom severity with scores below the median on the gait, balance, continence scales and on the mRS, were all separately associated with a higher mortality, as was a lower score on the MMSE. Patients who had suffered strokes or had a heart disease also had a higher mortality according to univariable analysis, as had male patients.

In the multivariable model, patients' age, sex, prevalence of heart disease and their scores on the gait scale and in the MMSE were all significantly associated with a higher mortality (table 8).

For each step, representing a more pronounced symptom degree on the ordinal scales of gait, balance and incontinence, as well as mRS and MMSE, a higher HR was found, illustrated by the Kaplan-Meier plots in figure 11. The only exception was score 7 in the continence scale, signifying indwelling urinary catheter – which is not a typical consequence of urologic disturbance in iNPH.

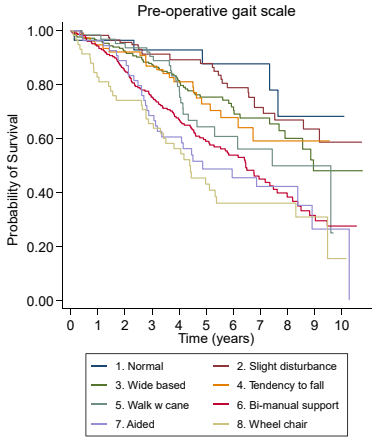
***Table 8**: Pre-operative variables' influence on survival in iNPH patients.*

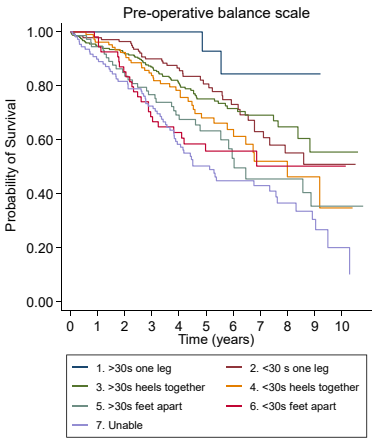
	Univariable Cox regression			**Multivariable Cox regression, significant covariates in model**		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age /10 years	1.99	1.70-2.33	<0.001	2.01	1.63-2.46	<0.001
Sex (male)	1.36	1.10-1.69	0.005	1.37	1.03-1.82	0.031
Hypertension	1.10	0.89-1.37	0.382		*not included*	
Diabetes	1.18	0.92-1.53	0.197		*not included*	
Stroke	1.54	1.17-2.04	0.002		*ns*	
Heart disease	1.66	1.32-2.09	<0.001	1.59	1.19-2.12	0.002
Claudication	1.91	0.60-6.02	0.271		*not included*	
Number of comorbidities	1.22	1.11-1.36	<0.001		*ns*	
Gait scale ≥5	2.20	1.75-2.77	<0.001	1.78	1.34-2.36	<0.001
Balance scale ≥4	1.98	1.54-2.53	<0.001		*ns*	
Continence scale ≥4	1.87	1.49-2.36	<0.001		*ns*	
mRS ≥3	2.23	1.73-2.87	<0.001		*ns*	
MMSE score/5 points	0.67	0.60-0.75	<0.001	0.77	0.68-0.88	<0.001

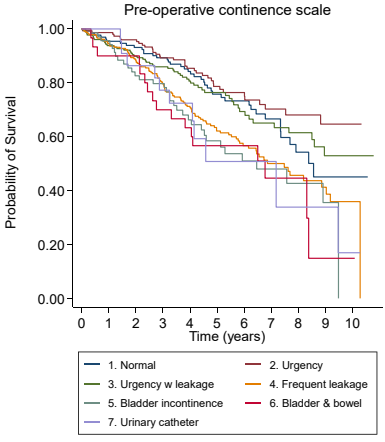
After re-setting the baseline of the analyses to the time of the postoperative examination, the influence of surgical outcome on survival was also analyzed. Patients who showed improvement in the gait scale or in the mRS, were found to have a lower HR for death, and this finding remained significant when adjusted for age, sex and prevalence of heart disease.

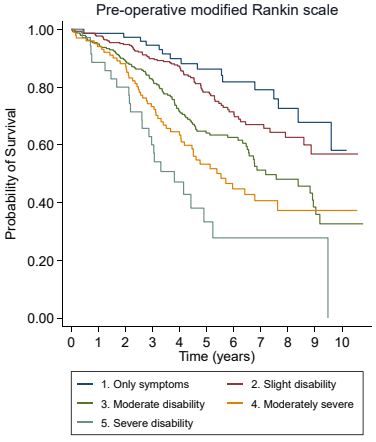
A comparison with the control group showed that patients who improved in both the gait scale and in the mRS (n=144) did not have an increased mortality compared to the general population, in contrast to patients who did not improve.

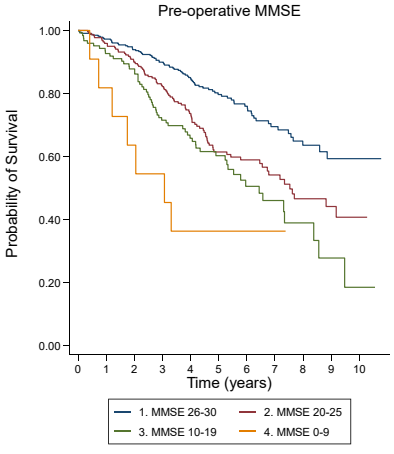
Figure 11 (opposite page): *Survival in iNPH patients based on preoperative symptom severity in the Gait scale, Balance scale, Continence scale, the mRS and the MMSE categorized into four groups as shown.*


Pre-operative gait scale
Probability of Survival
1.00
0.80
0.60
0.40
0.20
0.00
0 1 2 3 4 5 6 7 8 9 10
Time (years)
1. Normal
2. Slight disturbance
3. Wide based
4. Tendency to fall
5. Walk w cane
6. Bi-manual support
7. Aided
8. Wheel chair


Pre-operative balance scale
Probability of Survival
1.00
0.80
0.60
0.40
0.20
0.00
0 1 2 3 4 5 6 7 8 9 10
Time (years)
1. >30s one leg
2. <30 s one leg
3. >30s heels together
4. <30s heels together
5. >30s feet apart
6. <30s feet apart
7. Unable


Pre-operative continence scale
Probability of Survival
1.00
0.80
0.60
0.40
0.20
0.00
0 1 2 3 4 5 6 7 8 9 10
Time (years)
1. Normal
2. Urgency
3. Urgency w leakage
4. Frequent leakage
5. Bladder incontinence
6. Bladder & bowel
7. Urinary catheter


Pre-operative modified Rankin scale
Probability of Survival
1.00
0.80
0.60
0.40
0.20
0.00
0 1 2 3 4 5 6 7 8 9 10
Time (years)
1. Only symptoms
2. Slight disability
3. Moderate disability
4. Moderately severe
5. Severe disability


Pre-operative MMSE
Probability of Survival
1.00
0.80
0.60
0.40
0.20
0.00
0 1 2 3 4 5 6 7 8 9 10
Time (years)
1. MMSE 26-30
2. MMSE 20-25
3. MMSE 10-19
4. MMSE 0-9

4.4.2 Causes of death

The 30-day postoperative mortality was 0.5% (5 cases), and this was not significantly higher than in the control population counted from the patients' date of surgery (0.4%; n=22). None of these deaths occurred in direct relation to the operation. The patients died after 11-27 days and their underlying causes of death in the CDR were acute myocardial infarction (1), intracerebellar hemorrhage (1), perforated gastric ulcer (1) and NPH (2).

Cerebrovascular disease was almost twice as common a cause of death in iNPH patients than in controls as was dementia. In contrast, controls were almost twice more likely to succumb due to malignant diseases. Cardiovascular disease, other than cerebrovascular disease, was also a more common cause of death in controls (figure 12).

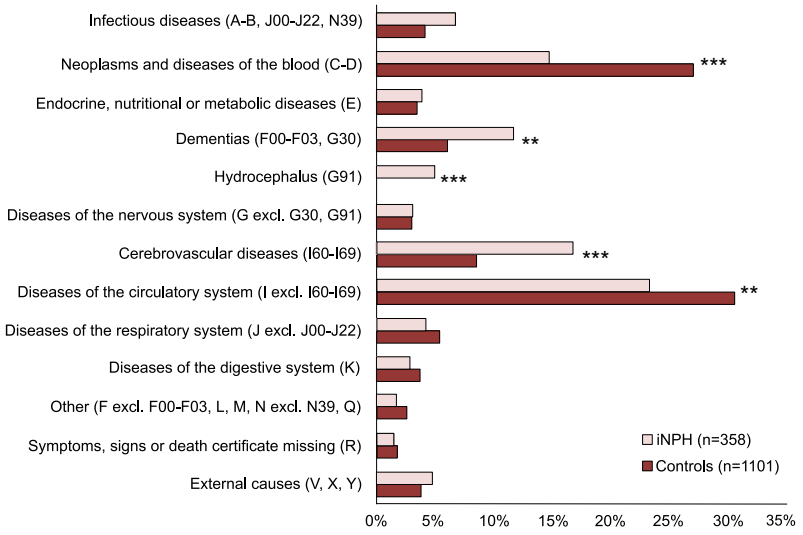


***Figure 12**: Underlying causes of death in 358 iNPH patients and 1101 controls from the general population. ICD-10 diagnostic codes are presented within parenthesis for each category.*
***p<0.01, ***<0.001*

5. Discussion

5.1 Natural course of iNPH

The course of symptoms in untreated patients was only scarcely described previously, and the effect of delayed compared to early surgery on treatment outcome or survival has never been reported. Paper I in this thesis shows that during a median of 13 months waiting time due to administrative and economic shortages in our hospital, the majority of iNPH patients deteriorated in their symptoms, with significant decline in gait, balance and cognitive abilities. Once treated, their symptoms improved to the same extent as for patients who did not have to wait, but the final outcome was less beneficial and their symptoms after treatment were not significantly different than at time of diagnosis, indicating that iNPH symptoms become increasingly irreversible in time. Further, their crude 4-year mortality was almost four-fold increased and adjusted mortality more than doubled.

The findings in paper I confirm findings from the few earlier studies in the literature describing the development of symptoms in untreated patients, where the majority of patients deteriorated, some as early as within 3 months[81, 171, 172, 174, 175]. In studies where the separate domains were individually reported, deterioration was described regarding gait and cognitive[81, 171-173] as well as urinary[81, 171, 173] symptoms. Of the earlier studies describing the course of symptoms in untreated iNPH, the majority reported patients who were not selected for shunt surgery, based on specific tests[81, 173-175]. Only two previous studies reported results from patients diagnosed with iNPH, of which four had accepted surgery and were re-examined while on the waiting list[172]. The remaining 19 refused shunt surgery, introducing another possible bias, as their unwillingness for shunt surgery might have been due to e.g. comorbid conditions or less severe symptoms[171, 172]. However, the 33 patients in paper I are unique as they were all - similarly as the contrast group of 69 patients diagnosed, accepted surgery, and all but one eventually underwent this treatment.

Further, as also seen in previous studies, not all patients deteriorated – instead the variations were unexpectedly large, with a change in iNPH scale ranging from +7 to -47. However, also the previous studies described that a subset of patients was unchanged, and even improvement was seen in up to 15% of patients after 3 months[81] to median 7 years[173]. In our study group of 33 patients,

improvement in the untreated phase was seen in 4 (12%). Possible reasons include improvement in other conditions, individual variations or physical training as all patients received physiotherapeutical advice at the time of diagnosis. However, paper I and the previous studies from the literature, clearly show that iNPH patients as a group progress in their symptoms with time.

The next aim was to compare the postoperative results of waiting patients with another group of 69 iNPH patients who had shunt surgery performed within 3 months from diagnosis. The magnitude of improvement in $iNPH_{Delayed}$ was shown to be similar as for $iNPH_{Early}$ in a PP analysis (per protocol: analysis of all available patients). However, in an ITT analysis (intention-to-treat: also lost patients counted) analysis the improvement rate was lower in $iNPH_{Delayed}$ than in $iNPH_{Early,}$ 48% vs 78%, (p=0.003). This was mostly due to more deceased patients in $iNPH_{Delayed}$, which is also considered a consequence of the wait with decreasing functions and increasing fragility. Compared to the second pre-operative investigation (pre-op 2) the total iNPH scale score, gait and balance subscores, MMSE and mRS improved after surgery in $iNPH_{Delayed}$ – but the iNPH scale subscores of neuropsychology and continence did not. As $iNPH_{Delayed}$ had deteriorated during the wait, the final outcome was less beneficial and their symptoms after treatment were not significantly different than at time of diagnosis.

After publication of paper I, one study confirmed the finding of less beneficial treatment outcome associated with longer waiting time for surgery[179]. These patients were not reassessed after waiting, meaning that their grade of improvement compared to just before surgery is not known, but it is plausible that this finding also represents partly irreversible symptom progression in iNPH.

The aim in paper II was to study the effect of delayed compared to early shunt surgery on survival, which has never been studied previously. In paper II, the 102 patients from paper I were followed up until their death or at least 4 years, the maximum follow-up time being 11.5 years. Mortality in $iNPH_{Delayed,}$ was increased by Hazard ratio 2.57 in a multivariable Cox regression analysis, including age, sex, symptom severity and comorbidities.

Reasons for the increased mortality in $iNPH_{Delayed}$ could be that – again – their symptoms increased, rendering them more disabled and fragile, and the pathological changes in iNPH with impaired brain perfusion and metabolism, were left without relief.

The effect of shunt surgery in iNPH has been questioned as controlled trials have been scarce[156, 213], although two randomized trials showed clear effects of shunting[110, 186]. Papers I and II add evidence that shunt surgery in iNPH patients has a real effect on the disease, as there were clear differences in outcome and survival between patients with direct or delayed shunt treatment.

5.2 Long-term outcome

The long-term outcome in iNPH is considered difficult to study, as these are older patients, mortality is high, comorbidities with functional effects on the same symptoms as caused by iNPH are common and increasing with time and age. Some authors have presented gloomy results of 15-33% improved patients in a long-term perspective[203, 201]. However, the systematic review by Toma published 2013 showed a pooled beneficial long-term outcome in 73% of patients after 3 years in studies published 2006-2010.

Our study with a uniquely large cohort of unselected iNPH patients reflecting every-day practise from centres all over Sweden, confirms the more positive view of more than 60% improvement on a long-term basis. Even if only some proportion of patients replied each year, altogether 64% contributed to the long-term results reported here. Each patient replied in median once to these follow-up letters, meaning that the different year groups are not to be considered as longitudinal follow-ups of the same small group of patients, but rather as different groups of patients replying at different time points. This should increase the generalizability of the results. Of these patients, up to 5 years after surgery, around 65% and after 6 years 55% were still subjectively improved.
The measurement of improvement in mRS was around 40% improved on a short- and long-term basis, but on a group level the smRS ratings were significantly better than pre-operative mRS only in the 2-year group, not in the 3-6-year groups.

The discrepancy in the two outcome measures is probably due to the mRS being rougher in several ways. First, patients may well have improved in a substantial way with ameliorations in mobility, ADL functions and quality of life, without shifting their mRS score. Second, the rating strategy is not the same in the preoperative assessment which is done in mRS by physicians, as in the long-term follow-up with self-assessments (smRS) by patients or their next-of-kin. However, although the mRS is in some way a rough measure, in two large

studies on iNPH as many as 69%[96, 147] of patients improved after one year. Those percentages are seen in specific studies with strict inclusion criteria and assumedly more stringent raters and better inter-rater reliability than in the registry study setting with an extensive number of raters. The inter-rater reliability for mRS in a study on stroke patients was only 43%[214], without the use of a structured interview, and no such strategy has knowingly been applied. One study from the Swedish national stroke registry showed that mRS scoring by a structured telephone interview is reliable[215]. However, validation of the use of mRS by patients themselves, smRS, has not been performed. Still, both the smRS and the general health assessment are considered valuable measures, representing outcome as experienced by the patients.

5.2.1 The influence of complications on the long-term outcome

The second aim of paper III was to study if complications leading to reoperations did influence the long-term outcome – and importantly they were not seen to impede improvement as no significant negative effects were observed. However, the reoperation rate within 10 years was rather high: 26%, of which 58% were performed within the first year of surgery. At least 14% of the patients had revisions due to mechanical problems. In the systematic review by Toma et al., the revision rate was 13% in 30 articles published after 2006. Most of those studies had a follow-up time of up to one year, while 42% of reoperations reported in paper III occurred later, and that is one explanation for the higher reoperation rate in paper III. Another explanation could be the unselected cohort of patients in the SHQR, compared to the often more carefully selected patients in specific studies. The infection rate of 6.4% is higher than in many other studies, where the average was 3%, but ranging from 0 to 10%[93].

Subdural hematoma (SDH) was reported in 4.5% of the patients in the review[93], which is in the same range as in paper III where the proportion was 3.7%. However, 3.7% only comprised those requiring surgical treatment, why the total frequency of SDH is higher. The earlier cited study by Gasslander[157] also reported the frequency of SDH in the SHQR, but from a larger cohort including the participants in papers III and IV. They found SDH in 10.4% of 1457 patients, and corroborating the finding in paper III, the frequency of SDH in need of surgical intervention was 3.5% in the SHQR.

5.2.2 The influence of vascular risk factors and vascular comorbidities on the long-term outcome

Paper III also aimed to study the effect of vascular risk factors and vascular comorbidity on long-term outcome. The rationale for this research question was that others had described less beneficial long-term outcome in patients with cerebrovascular comorbidity, and that vascular risk factors have been shown to be common in iNPH patients[43, 45]. Although vascular risk factors (as opposed to cerebrovascular comorbidity) have previously not been shown to influence the short-term outcome[147, 166, 170] – it was unknown if they result in a more progressive state of symptoms in treated iNPH patients with these factors present, and no previous study looked into their influence on the long-term outcome.

Earlier studies showed a less favorable outcome for patients with established cerebrovascular disease, defined as a history of stroke, infarctions on radiological imaging, or moderate to severe white matter lesions on a CT scan with 52% compared to 79% improved patients in the short term[166] and 49% vs 79% improved in the long term[170].

The result of paper III was that diabetes, heart disease, and a history of stroke were each associated with higher mRS scores at baseline, and the latter also after 3 years. However, neither of these three, nor hypertension, had a negative influence on the degree of postoperative improvement until 5 years after surgery. After 6 years, patients with earlier strokes or with hypertension had a less beneficial outcome regarding comparisons between their smRS and their preoperative mRS. At no time point, the prevalence of hypertension, diabetes, heart disease or previous strokes influenced how patients assessed their health condition – improved, unchanged or worse. In conclusion, these factors had only minor influence, which indicated that patients with these risk factors or comorbidities benefit equally from shunt surgery as patients without these factors at least until 5 years after surgery, and should also be equally eligible for shunt surgery.

5.3 Survival and causes of death in iNPH

5.3.1 Survival

Paper IV aimed to describe survival in treated iNPH patients in a large registry-based study with 979 iNPH patients from the SHQR with up to 10 years follow-up, compared to the general population and analyse how survival is influenced by different factors – a topic which has not been thoroughly studied previously. The mortality in treated iNPH patients in paper IV was 1.8 times increased compared to the general population, thus lower than in earlier studies published in 2000 (relative risk 3.3)[197], 2006 (Standardized Mortality Ratio 2.5)[199] and 2007 (7.4% observed compared to 3.2% expected deaths)[178]. This discrepancy could be partly due to different statistical methods and group sizes. However, it may also partly be explained by an increasing awareness of iNPH leading to earlier diagnosis, and/or to improved medical care for these patients as well as continuously improved primary and secondary prophylactic treatments for patients with vascular risk factors which are over-represented in these patients.

The diagnostic procedure in the study by Jaraj[184] was not similar as those applied in this thesis. But, as expected, the untreated probable iNPH patients in that study had a higher mortality compared to controls, HR 3.8. Even if these results are not directly comparable to paper IV, where HR for treated iNPH patients compared to the general population was 1.8, these findings altogether imply that shunt surgery increases survival in iNPH patients. Further the findings in paper II where delayed surgery decreases iNPH patients' survival, strengthens this conclusion.

The effect of symptom severity on survival has previously not been studied. In paper IV, more advanced symptoms were associated with higher mortality. This association was found for all symptom grading scales, but in the multivariable analysis the gait scale and the MMSE stood out as the most important factors. This is not surprising as patients with more symptoms have more advanced disease, probably also more frequently concomitant diseases and are more fragile. One previous study from Finland looked into the influence of vascular risk factors and vascular comorbidities on survival in iNPH patients, describing higher mortality in patients with chronic heart failure or diabetes type 2[11]. In paper IV the more unspecific entity of "heart disease" was shown to be associated with a higher mortality, while diabetes, hypertension, previous strokes and claudication were not. Further, the Finnish study did not find any sex

difference, but paper IV showed an increased mortality for male compared to female iNPH patients.

Patients who improved in the gait scale and in the mRS subsequently survived longer than patients who did not improve in these scales.
A similar finding was reported by Mirzayan: patients who survived until 5 years postoperatively, had previously shown larger improvements in the short-term evaluations[200].
In fact, in paper IV, the 144 patients who had improved in both the gait scale and the mRS, did not have a higher mortality than the general population in a multivariable analysis adjusted for the known significant covariates age, sex and heart disease.

Fourteen % of the patients instead deteriorated in the gait scale (98/691) and 14% in the mRS (85/624), and their mortality was higher compared to improved or unchanged iNPH patients and compared to controls (HR 2.69, 95% CI 2.00-3.69 and HR 2.62, 95% CI 1.9-3.62, respectively, both $p<0.001$). One possible cause for their deterioration as well as higher mortality, could hypothetically be progressive vascular ischemic changes – but this was not supported in the analyses of existing data. No difference in the prevalence of vascular risk factors or comorbidities (hypertension, diabetes, stroke, heart disease or claudication) was found between improved, unchanged or deteriorated patients in the gait scale or in the mRS. Further, there were no sex differences and only minor age differences (patients who were postoperatively improved, unchanged or deteriorated in the mRS were aged in median 73, 75 and 74 years respectively, $p=0.008$ and no age differences were seen in patients who were improved, unchanged or deteriorated in the gait scale). In conclusion, probably other unknown factors e. g. concomitant neurodegenerative diseases, explain the deterioration and higher mortality in these patients.

5.3.2 Causes of death

Causes of death in iNPH patients were for the first time compared with the general population in paper IV. The findings largely confirm those impressions given by earlier studies. Cardiovascular and cerebrovascular diseases were the most common causes of death in iNPH patients, while death due to malignancies was less common. In controls, cardiovascular disease was also the most common cause of death, tightly followed by malignancies. Deaths due to cerebrovascular diseases were only half as common in controls as in iNPH patients.

As vascular risk factors are common in iNPH patients[43, 45] and associations between arterial hypertension and the development of ventriculomegaly have been established[46, 161], it is assumed that iNPH and cerebrovascular disease share some pathophysiological mechanisms. But it is unknown if also the hydrocephalic state contributes to aggravation of the blood vessel impairment.

There is no probable biological explanation to malignancies being less threatening to iNPH patients. Instead, a negative selection bias for referrals to hydrocephalus teams, and the iNPH patients' shorter life expectancy with less time to develop malignancies, are plausible explanations for this difference.

Dementia was the fourth most common cause of death in both groups, but not unexpectedly, almost twice as common in iNPH patients. Some of these patients were demented already at time of diagnosis. In spite of responding to treatment in the study by Koivisto, 46% developed dementia in the long term, mostly diagnosed as AD or vascular dementia[216].

The size of the study group in paper II is probably too limited to adequately detect differences, however one statistically significant difference was in fact found. The proportion of patients who died due to malignancies was lower in $iNPH_{Delayed}$ (0/17 vs 4/16, p=0.044). This could possibly also be explained by the fact that they lived shorter and had less time to develop malignancies.

5.4 Comments

The demonstrated symptom progression over time in paper I, with increasingly irreversible symptoms, in conjunction with the finding in paper IV of a higher symptom burden being associated with a higher mortality, and that patients with better postoperative results survived longer – together lead to the inference that early diagnosis and treatment are crucial, in order to optimize the short- and long-term benefit as well as survival.

None of the studies in this thesis were designed for, and cannot elucidate, *how early* is the optimal time point of treatment. One previous study including 17 adult patients with congenital "asymptomatic" or "compensated" hydrocephalus with no or mild symptoms, showed that 16 patients improved by surgery[217], but it is unknown if the same applies for older persons with late debuting iNPH.

Although studies showed that the prevalence of complications is decreasing[93, 158], paper III unfortunately confirms that these are still common. More than every fourth patient required renewed surgeries for different reasons. Therefore, the risks and benefits must be carefully weighed when making the decision of shunt surgery. The costs in form of suffering for patients and their families, and the resources demanded to deal with these complications are in no way negligible. However – importantly, paper III did not show that shunt complications had any negative effects on the long-term outcome.

It appears plausible that in 3-4 years' time, a progression in symptoms occur in some patients, and to a larger extent in those aged 80 years or above, as illustrated by the figures by Liu and Takeuchi, although in those studies not reaching or exceeding the preoperative level. None of the recent studies on long-term outcome showing progression in symptoms[190-192], made any comments about the expected course without a shunt[176, 218]. According to the findings in paper I, iNPH patients without treatment for 13 months, progress in their symptoms. Consequently, with a shunt, in case of future deterioration, patients will be at a better starting point if surgery is not postponed. Moreover, perhaps it is not surprising that symptoms do progress to some extent especially in the elderly, and turned around, also minor remaining treatment gains might be of relevance to patients' daily life and ADL functions. For comparison, even the small effects seen by 30 weeks of acetylcholine-esterase inhibitor pharmacotherapy in AD patients, could prevent nursing home placement[219]. An additional 2.2 life years and 1.7 QALYs was calculated to be added by treatment in iNPH patients' lives, which is remarkable for a patient group of high age, and the cost-benefit has clearly been shown to be in favour of surgery[151, 152].

5.5 Limitations and strengths

5.5.1 Papers I and II

The main limitation of the natural course papers (papers I and II) is the age difference between the two groups. The initial plan was to make a head-to-head matching of patients from the database for each of the 33 patients in the delayed group. However, attempting this, it was discovered that there were not enough older persons with early surgery in the database, meaning that unintentionally and unawarily, some of the oldest patients had been forced to wait for a longer

time. Instead, as described in the methods section, all available patients in the database with a short waiting time, were included.

In paper I, no statistical method allowing for age adjustment was performed, but no significant correlations could be seen between the patients' age and their development on the iNPH scale. Additionally, when post-hoc complementing these tests with an explorative logistic multivariable regression model including age, the waiting time was shown to be associated with higher odds for not being improved postoperatively, while the patients' age was not.
The statistical analyses in paper II were adjusted for this difference by using a Cox regression model where age was included, and by calculating Kaplan-Meier curves after exclusion of patients to create groups without significantly separated medians and the same age range.

One possible cause for the unintentional negative selection of older patients could be that these patients or their relatives, were less prone to repeatedly contacting the operation coordinator to stress the importance of not postponing surgery. iNPH symptoms tend to be more accepted in older persons than in younger, thought also to be caused by the persons' age.

The study was not randomized, but instead based on external circumstances that randomly allocated patients, due to a natural experiment. Such circumstances are unwanted and will hopefully not occur again, meaning that they were also unique, from a scientific point of view. In contrast to the previous studies where data from unshunted patients are presented[81, 171-175], all patients were examined, diagnosed and treatment decisions were made in the same way according to the same criteria and all but one eventually received shunts.
Altogether, the observational design is a limitation – but designing an interventional randomized study with the same length of follow up would not be ethically defendable. Given the random circumstances, the group of 33 patients is thought to be representative for iNPH patients, therefore the descriptions of their natural course and less beneficial outcome after waiting can be considered valid and generalizable for other iNPH patients.

Another strength is that all patients were thourougly examined by neurologists, neuropsychologists, neuroradiologists and physiotherapists. The examiners were not blinded, evidently, which is a limitation – but blinding would have been impossible as these data were collected from patients in routine care.

Another limitation is the relatively small sample size, but altogether the study group of 102 patients is larger than many studies on iNPH as shown in the long-term follow-up studies listed in tables 1A and 1B.

In addition to the strengths listed above for paper I, paper II had a long follow-up time of more than 5 years. The primary outcome measure was mortality, meaning that no subjective or observer biases and no placebo effects were possible, and the use of CDR data means there was no loss of follow-up.

5.5.2 Papers III and IV

Regarding paper III, as mentioned, the incomplete number of questionnaire responses, ranging from 17% in the 6-year group to 33% in the 2-year group, constitutes the major limitation. Sixty-four % (623 patients) contributed at least once in the long term follow up (447 replied once, the remaining 176 twice or more). Of the 358 patients (37%) that were lost to long-term follow up, 67 were deceased at the time of the two years' follow-up and 31 declined participation. There was no information about long-term follow-ups for the remaining 260 patients in the SHQR at the time of data extraction in 2014. The most probable cause of the loss of follow up is staff shortage in several centres in periods, as each centre has been responsible for sending long-term follow-ups to their respective patients. Other possible explanations include patients forgetting or being unwilling to return the questionnaires. A selection bias cannot be ruled out, but could effect the results in two ways. On one hand, improved patients might have been more prone to reply to these questionnaires – on the other hand, patients without improvement might have wanted to signal this by replying.

Noteworthily, per each year group, there were no differences regarding baseline findings or having had complications or not, between patients who did or did not provide filled out questionnaires - with one exception. In the two years' group, repliers had to a lesser extent undergone reoperations (18% compared to 27%, p=0.004).

Turned around, the number of existing data on long-term follow-ups in the study, is vast, and internationally unique in size for this patient group (tables 1A and 1B). The work that has been done by register holders and register secretaries to collect all this data – is extensive. The collection of this large number of follow-ups would not have been possible in any other way. The economic and staff capacity that clinical visits or even telephone follow-ups would have

demanded, have not been procurable. One additional advantage of posted questionnaires is that patients were in no way influenced by an examiner when providing data.

The major strength of paper III is that it is a quality registry based study, allowing for a uniquely larger sample size of 979 patients, with data collected prospectively up to 10 years. Patients were diagnosed and treated according to clinical everyday routines without addition of specific inclusion or exclusion criteria, such as often applied in other studies, meaning that the cohort studied better reflects the target population.

The same strengths can be listed for paper IV where these 979 patients' survival was studied. Further advantages, are as in paper II, that the outcome measure studied was survival – a completely objective and unbiased measure, without loss of follow-up as data were again commissioned from the CDR. Another strength in paper IV is the use of a large control group from the general population where the matching procedure was done by the governmental bureau Statistics Sweden.

The CDR also provided information on the causes of death for deceased patients, which is also a strength. However, the reliability of these data are limited by the fact that in many cases the ultimate cause of death is not always evident for the physician filling out the death certificate form. If no autopsy is undertaken, known conditions before the time of death must be taken into consideration, along with conclusions from the course of symptoms leading to death. The autopsy rates have dropped during the past decades. On the other hand, the diagnostic capacity in vivo has increased, and e.g. undetected malignancies are probably less common. The uncertainty has been found to vary with the deceased persons' age and reported causes of death – higher for older persons and for chronic diseases.[220]

In this thesis, the applied method was to report the underlying cause of death, as registered in the CDR, in all cases, in both papers II and IV – therefore allowing for some degree of inference.

5.6 Proposed model of the disease course in iNPH

The natural course of iNPH can, based on the findings in this thesis, be summarized in a hypothetical model (Figure 13). The trigger for disease is unknown, but underlying mechanisms, e.g. arterial hypertension[161], vascular disease mechanisms[43], leptomeningeal changes[35], congenital factors[54], genetic predisposition[56] or ciliary dysfunction[59] give rise to hydrodynamic disturbance, causing the morphology of the brain and ventricular system to change. High convexity sulci are pressed together, followed by ventriculomegaly starting in the largest portion which is the frontal horns, then to engage occipital and finally involve the temporal horns, as well as the third and fourth ventricles (*green dotted line: "Ventriculomegaly"*)[180, 181]. These morphological changes are not alone sufficient to cause symptoms[9, 182] although the glucose consumption is lowered[183]. Added, probably secondary, factors cause disturbance of the microcirculation with chronic ischemia in the periventricular white matter, and disturbed turnover of metabolites[136], giving rise to functional metabolic effects on the brain (frontal lobes, periventricular areas, aqueduct-adjacent brainstem structures)[48].

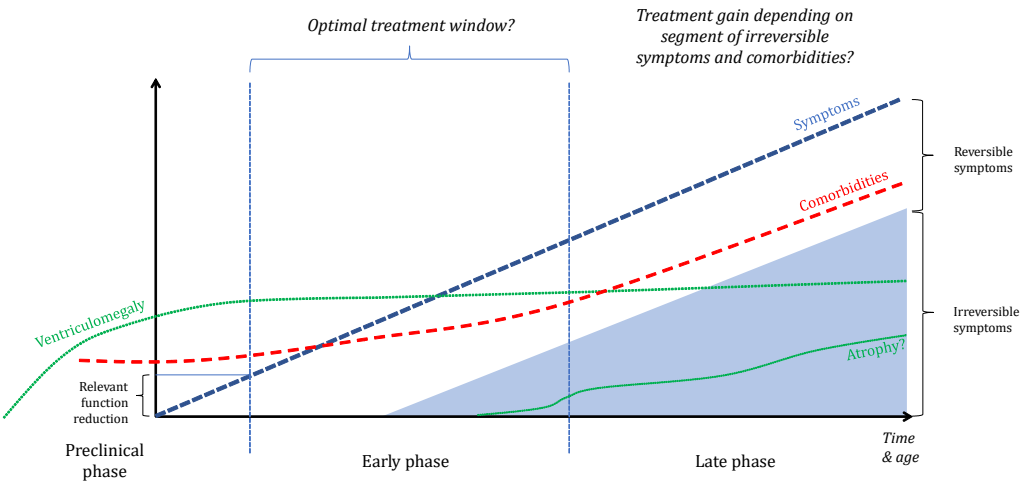


Figure 13: *Model of the natural course in iNPH.*

As symptoms start to develop they are mild, but slowly increasing in a chronic progressive way (*blue dashed line: "Symptoms"*). The rate of increase appears to be individual with a large range[176, 218] (as shown in paper I). The time axis in the hypothetical model ranges individually from a few years to a couple of decades. Initially, during the early phase of symptom development, hypothetically the symptoms are reversible. However, as the disease course progresses, irreversible pathological changes take place – e g chronic ischemic and metabolic changes, disturbed glymphatic clearance[29] eventually resulting in neurodegeneration (*green dotted line: "Atrophy?"*) and a portion of the symptoms are no longer reversible *(light blue field)*.

At the same time as these pathological changes occur and as age increases, most persons suffer from a range of diagnosed or undiagnosed comorbidities *(red dashed line)*, often giving rise to similar symptoms (unspecific symptoms such as tiredness, mental blunting and exhaustion from physical activity, or more specific like gait and balance disturbances, urinary symptoms)[160], in some instances constituting larger functional reductions than the hydrocephalus. How much each factor contributes is not always possible to elucidate. Increasing severity of cardiovascular and pulmonary diseases also eventually limits the possibilities for safe treatment, as the gold standard is surgery.

According to this hypothesis, the optimal treatment window occurs when symptoms cause enough function reduction as to motivate taking the risk and inconvenience of surgery (at the individual patient and neurosurgical care provider's apprehension) – before the (unknown) proportion of irreversible symptoms becomes large. To date, there is no way to adequately assess when this optimal treatment window occurs or to adequately predict the treatment effects.
However, according to this model, based on findings in paper I where also patients who had deteriorated after waiting improved, there is no "point of no return" where there is no longer any possible treatment gain – but the improvement potential and possible benefit of treatment is decided or hampered by the amount of comorbidities, accumulation of irreversible symptoms and unknown factors.

Another possible contributing factor to symptoms perceived as irreversible, not shown in the figure, is *habit* where it has been shown that patients although improved in their ability to walk and perform different activities, are not spontaneously prone to increase their level of physical activity[221], their everyday environment having been adapted to not needing to be physically active.

Further, from a pathophysiological point of view, the limited predictive value of hydrodynamic tests, can be seen in this model as the effect of demonstrable hydrodynamic disturbances being present in the preclinical and early phase but ebb away as other secondary effects dominate in the late phase[171]. Still, deviation of CSF can alleviate effects of the microcirculatory and metabolic disturbances in the brain at the later stages[110, 116]. Shunting immediately changes the absorption mechanism and thereby "eliminates" both the vascular and hydrocephalic component of the disturbed CSF dynamics, as well as improves periventricular perfusion[116].As the effect of the shunt is permanent it may even compensate for the deterioration known to be associated with hypertension and diabetes and thereby explain the lack of negative long-term effects[222].

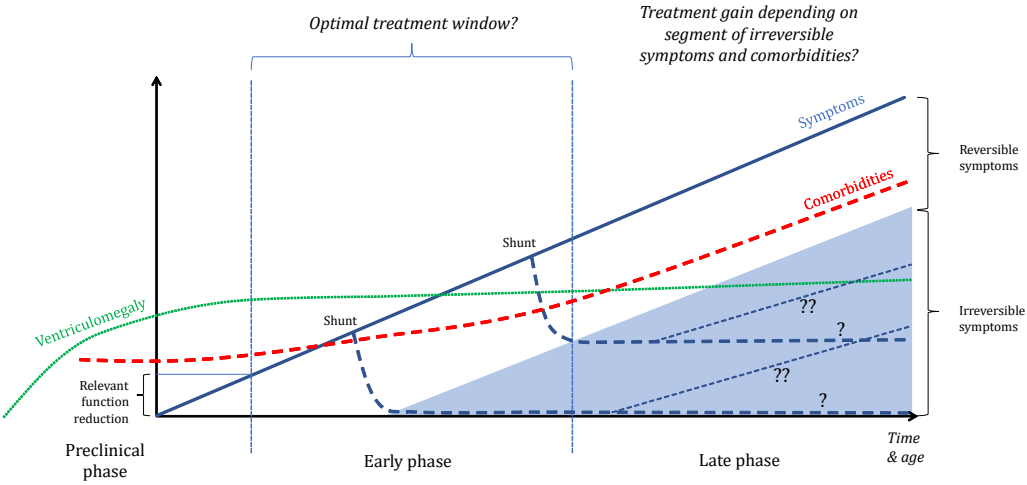


Figure 14: *Model of treatment effect and long-term outcome in iNPH.*

The second hypothetical model (figure 14) shows the short- and long-term effect with symptoms diminishing after shunt surgery. Patients who have not yet accumulated an irreversible segment, have the potential of complete relief of symptoms (*lower blue dashed line, "?"*). On the other hand, patients who have developed a portion of irreversibility, which is presently the majority of patients[77], will be improved but with remaining symptoms (*upper blue dashed line, "?"*).

It has been suggested, that the hydrocephalic symptoms later progress in spite of functioning shunts (*symptom trajectories marked by "??"*)[190, 192, 201, 216].However, there is no evidence that this late deterioration is in fact caused by the hydrocephalic state *per se*, rather than coexisting pathological processes. There are several other possible explanations for lack of sustained clinical and functional response:

- Co-presence of another neurodegenerative disease present at time of diagnosis or presenting later, e.g. AD[190, 216].
- It has also been suggested that neurodegenerative diseases that mimic iNPH and give rise to ventriculomegaly can have symptoms shortly responding to shunt treatment[188, 223]. The possible alternative explanation for these findings is that those patients had two comorbid conditions. This appears unlikely if both are considered extremely rare – but iNPH is not extremely rare[9].
- Progress of chronic ischemic damage due to small vessel disease – which is commonly present in iNPH brains – which is thought to cause or contribute to the hydrocephalic state, and entails similar symptoms. However, presence of vascular risk factors or vascular comorbidities including manifest cerebrovascular disease at the time of iNPH diagnosis, could not be shown to influence the long-term outcome until 5 years after surgery in paper III.
- Deterioration caused by other comorbidities frequently seen in these patients[160]. Of those 482 patients studied by Takeuchi, it is stated that in all cases, those patients without retained improvement after 4 years, had deteriorated due to comorbidities or age related changes[192].
- The effect of *age* in a brain with previous hydrocephalic damage is not known. In parallel to e g post-polio damages becoming more disabling with increasing age due to age related motor neuron loss, hypothetically the same could be seen in brains treated for hydrocephalus: partly irreversible remaining damage, becoming functionally more evident in combination with progressive age-related changes.
- Impact of surgery-related complications on functional status[203]. This notion could not be supported in paper III, although, in line with the findings in paper I it is plausible that patients with long lasting shunt dysfunctions will have less reversible symptoms once their treatment is resumed.
- Undetected shunt failure or not optimally set shunt valves, where later adjustments have shown effect in some patients[193]. However, in studies describing patients with delayed progression, authors argue that there

were no signs of non-patent shunts and that changing the shunt valve only gave short-lasting effects[190, 216].

- A temporary placebo effect[224]. The only double-blinded RCT[110] shows that this is not an important issue.

Further, according to the findings in this thesis and according to the model, if late deterioration in fact occurs in treated patients, the starting point for that deterioration is more beneficial if surgery is performed at an earlier stage.

6. Conclusions

This thesis concludes that:

1. The natural course of iNPH is symptom progression over time, with worsening in gait, balance and cognitive symptoms. This deterioration is only partially reversible. To maximise the benefits of shunt treatment, surgery should be performed soon after diagnosis.
2. During a follow-up of more than five years, patients whose treatment had been delayed by 6-24 months had a more than two-fold increased risk of death. Shunt surgery is effective and early treatment increases survival.
3. Around 65% of iNPH patients were subjectively still improved 2 to 5 years after surgery, and 55% after 6 years.
4. No negative impact of complications and only minor effects of vascular comorbidity could be seen on the long-term outcome in iNPH patients in a registry-based setting.
5. Mortality is 1.8 times higher in treated iNPH patients compared to the general population.
6. Death due to cerebrovascular disease is common in iNPH patients, while death due to malignancies is less frequent than in controls.
7. Preoperative symptom severity is linked to mortality, especially for gait and cognition (MMSE).
8. Postoperative improvement in gait or in functional independence (modified Rankin Scale) is associated with longer survival.
9. The survival of iNPH patients who improve in both an ordinal scale of gait, and in the modified Rankin Scale, is similar to that of controls from the general population, indicating that shunt surgery for iNPH besides improving the symptoms and signs, can normalize survival.

7. Future Perspectives

Considering that life expectancy is rising, the number of persons with iNPH might be increasing. As treatment of iNPH has shown to be beneficial to patients' functions, with decreasing disability, increasing quality of life and increasing life expectancy, it is important to find and diagnose patients with this condition – not to miss the opportunity of an effective treatment given at a relatively low cost. Further, it is of value to find and diagnose these patients already in the early phase, as more advanced symptoms were shown to be associated with a higher mortality, and that symptoms are progressive and only partially reversible. Unfortunately, the condition remains under-diagnosed.

It is important to keep increasing the awareness of this condition, which appears to still not well enough known by the population or by primary health care physicians nor physicians in general. Other key professionals with the possibility of initiating the suspicion of iNPH are radiologists. The knowledge of radiologists in general about typical morphological findings in iNPH probably needs to increase. Many older persons are subject to brain CTs or MRIs, for different reasons. In situations where the indication of brain imaging is evaluation of iNPH typical symptoms, where the referring physician indicated that one of the purposes of the radiological examination was to look for iNPH typical findings, that specific question will be assessed. However, among physicians working with evaluation of iNPH patients, it is not uncommon to find that patients had earlier performed brain CTs due to other indications such as head trauma, strokes or TIAs, and that morphological signs of iNPH had already been present but not commented by the radiologists, and retrospectively also clinical signs might have been present.

Further, there is a pressing need for development of more reliable markers of diagnosis and prognosis. The challenge of diagnosing iNPH remains not to miss the opportunity of effective treatment, but also to not expose persons without benefit of shunt surgery to the surgical risks. If the diagnostic process was more exact and easier accessible, probably the proportion of persons with iNPH who gets diagnosed, would increase. One key to better diagnostic tests, is to better understand the pathophysiological mechanisms. Further, probably the entity of iNPH needs to be better subcategorized, as there are indications to different initiating factors and as the neuropathological studies show diverse findings.

However, the potential of developing simple accurate tests should not be over-estimated, as there will probably always be a risk of comorbid factors constituting a larger cause of disability than assumed, and the individual assessment of combination of symptoms and signs with evaluation of contributing factors as well as expectations, will remain crucial in the treatment decisions.

Next, even if this thesis could not show that shunt complications leading to re-operations impaired the long-term results, it also showed that complications to shunt surgery are still common. The risk of complications constitutes an obstacle for offering this treatment. The scientific community, neurosurgical centers and the medical-technical industry need to make individual and cooperative efforts in finding ways to reduce shunt complications. Further, alternative treatment options with less complications need to be explored, such as other types or locations of surgical shunts, or pharmacological treatments. Rehabilitation might be important, also in combination with standard shunt treatments to maximize the individual improvement potential.

Future long-term studies should look further into why some patients deteriorate in the long-term, and what factors are important for good outcomes – this is important information in the treatment decision and for adequate information to patients and their families.
Another important research question is to analyze when is the optimal time point of treatment. Is there a risk of later deterioration also for patients with early treatment who experience complete symptom relief – or are they "cured"? However, the use of RCTs where patients are randomly assigned to postponed surgery to evaluate the correct time point of treatment are ethically questionable, with the now existing evidence of the only partially reversible progressive disease course. Such studies would probably have to investigate patients who themselves choose to wait to have treatment – although this introduces a bias as those patients are e.g. less affected by their symptoms or for other reasons not willing to take the risk of surgery.

A follow-up study with regard to survival in iNPH patients randomized to delayed surgery would be of interest. The study by Tisell[110] probably included too few patients to detect any difference in mortality after 3 months' wait. Moreover, the question is if three months would be enough to see this effect. But if a difference in survival can in fact be seen between the groups in the randomized SINPHONI-2 study[186], this would certainly imply that earlier shunt surgery has a better effect, even than after treatment delayed only by 3 months.

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Appendix

The SHQR enquiry 2004-2014 for follow up of patients operated for hydrocephalus, translated from Swedish

How are you feeling now, compared with your condition before surgery?

❑ Better ❑ Unchanged ❑ Worse

The following questions are about different functions that are often afflicted in the condition you were treated for. Indicate which box you think best applies to your condition during the last month.

Walking	❑ No problems	❑ Some problems	❑ Severe problems

Do you use walking aids? ❑ Yes ❑ No

Walking aids	❑ cane	❑ indoors	❑ outdoors
	❑ crutches	❑ indoors	❑ outdoors
	❑ roller	❑ indoors	❑ outdoors
	❑ wheelchair	❑ indoors	❑ outdoors

Memory	❑ No problems ❑ Some problems ❑ Severe problems
Bladder	❑ No problems ❑ Urgency but no leakage ❑ Sometimes leakage of urin, do not use diaper ❑ Often leakage of urin, always use diaper ❑ Always leakage of urin, always use diaper ❑ Leakage of urin and faeces ❑ Urinary catheter
Disability/need for assistance	❑ None ❑ Some problems that do not restrict my life style ❑ Minor disability, some restrictions to my lifestyle, no need for assistance ❑ Some disability, which clearly restricts my lifestyle, need for assistance ❑ Severe disability, dependent but not in constant need of assistance ❑ Very severe disability, in need of constant care, day and night

Contacts with doctors

Have You had any appointment with a doctor during the last year? ❑ Yes ❑ No

❑ General practitioner ❑ Internal medicine ❑ Surgeon

❑ Geriatrician ❑ Other:_____

If you wish, you may explain why:

_____

The form was filled out by:_____

Relation to patient:_____

Signature:_____ Phone nr:_____

Room for comments:

_____

_____

❑ I do not wish to receive any further follow-up letters