Idiopathic Normal Pressure Hydrocephalus

Aspects on Pathophysiology, Clinical Characteristics and Evaluation Methods

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Läraren lever och lär och läraren lär lära så länge han lever av sina elever, vilka lättare lär lära den lära han lär om läraren lär som han lever.

Alf Henriksson
(1905-1995)
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LIST OF PUBLICATIONS

Reduced Thalamic NAA in idiopathic Normal Pressure Hydrocephalus
A Controlled $^1$H-MRS Study of Frontal Deep White Matter and the Thalamus Using Absolute Quantification.

Pre-Postoperative $^1$H-MRS-Changes in Frontal Deep White Matter and the Thalamus in idiopathic Normal Pressure Hydrocephalus.
Submitted to J Neurol Neurosurg Psychiatry

III. Lundin F, Ulander M, Svanborg E, Wikkelso C, Leijon G.
How Active are Patients with idiopathic Normal Pressure Hydrocephalus and does Activity Improve after Shunt Surgery? A Controlled Actigraphic Study.

IV. Lundin F, Ledin T, Wikkelso C, Leijon G.
Submitted to Clin Neurol Neurosurg
ABSTRACT

Introduction.
Idiopathic normal pressure hydrocephalus (iNPH) is a condition with enlargement of the cerebral ventricular system and an intracranial pressure (ICP) within normal limits. Cerebrospinal fluid circulation is disturbed but the mechanisms behind the symptoms: gait and balance difficulties, cognitive dysfunction and micturition problems, are as yet mostly unexplained.

Aim.
In Studies I and II the aim was to investigate cerebral metabolism in the frontal deep white matter (FDWM) and the thalamus in iNPH using Magnetic Resonance Spectroscopy (MRS) before and after shunt surgery and to compare this with healthy individuals (HI). In Study III the aim was, by use of actigraphy, to measure motor function, energy expenditure and resting/sleeping time in iNPH patients before and after shunt surgery, in comparison with HI. In Study IV the aim was to study postural function using computerised dynamic posturography (CDP) before and after shunt surgery as well as in comparison with HI.

Patients and Methods.
In all studies the patients had a neurological examination and baseline bedside assessments of motor, balance and cognitive function were performed. Motor function was assessed using a motor score (MOS) consisting of the following items: 10 metre walk time in seconds and number of steps and TUG time in seconds and number of steps. MOS was considered significant if there was an increase of 5% or more. The HI were also tested for motor, balance and cognitive function. In Study I the patients (n=16) and the HI (n=15) were examined with MRS (absolute quantification) with voxels placed in the thalamus and in FDWM and compared with one another. In Studies III and IV the preoperative results of actigraphy and CDP respectively in patients (Study III n=33; study IV n=35) were compared with the HI: Study III, n=17; Study IV, n=16. The HI performed these examinations twice and the average was calculated. In Study II, 14 patients, and in Studies III and IV, 20 patients underwent shunt surgery and new MRS/actigraphy/CDP examinations were performed three months postoperatively and compared with the preoperative results.
Results.

In the patients decreased total N-acetyl compounds (tNA) and N-acetyl aspartate (NAA) were found in the thalamus compared to the HI. No metabolic differences were seen in the FDWM between the groups. Postoperatively there were no metabolic changes in the thalamus but an increased total Choline (tCho) and a borderline significant decrease in myo-inositol (mIns). During the day the patients took fewer steps and had also lower total energy expenditure (TEE) than the HI. There was no difference concerning resting/sleeping time between patients and the HI. Postoperatively there were no differences of either number of steps, TEE or time spent resting or sleeping compared with the preoperative state.

Postural function was worse in the patients compared to the HI, this difference being more pronounced in tests measuring vestibular function, where loss of balance (LOB) was frequent. There was only a slight improvement in balance after shunt surgery. A positive response to the shunt operation was seen in 86% in Study II, 85% in Study III and 90% in Study IV.

Conclusions.

Our results suggest that the thalamus may be involved in the pathogenesis of iNPH. In contrast to others, we did not find any metabolic abnormalities in the FDWM, nor detect an increment of tNA or NAA postoperatively in the thalamus. The postoperative increase in tCho and borderline decrease in mIns in the FDWM might reflect a state of metabolic recovery since high tCho, a major component of the cell membrane, may be a sign of increased membrane turnover, and a decrease in mIns may indicate diminished gliosis.

The low gait capacity seen in the iNPH patients was not surprising but well that time spent resting/sleeping did not differ from the HI. Another unexpected finding was the unchanged ambulatory activity after shunt surgery despite improvement in a point test to determine capacity to walk a short distance. We believe this could be due to strong habits that are difficult to break and/or shortage of rehabilitation after surgery.

There was a profound postural dysfunction in the patients with many falls, especially in test situations intended to measure vestibular function. This implies that there is a central vestibular disturbance. The discrete improvement in postural function postoperatively was lower than previously reported.
SAMMANFATTNING

Bakgrund.
Idiopatisk normaltryckshydrocefalus (iNPH) är ett tillstånd karaktäriserat av ett förstorat ventrikelsystem i hjärnan trots att det intrakraniella trycket är inom normala nivåer. Det föreligger en störd omsättning av cerebrospinalvätska men de bakomliggande mekanismerna som leder till symptomen: gång och balansvårigheter, kognitiv nedsättning och problem att hålla urin, är fortfarande till största delen oklara.

Syfte.
I studie I och II var syftet att undersöka ämnesomsättningen i den djupa vita substansen i frontalloben (FDWM) och i thalamus hos iNPH patienter med magnetkameraspektroskopi (MRS) före och efter shuntoperation och jämföra med friska kontrollpersoner (HI). I studie III var syftet att med aktigrafi undersöka gångförmågan under lång tid, energiförbrukningen och vilo- och sovtid i patientens hemmiljö före och efter shuntoperation samt jämfört med HI. För studie IV var syftet att undersöka balansförmågan med datoriserad dynamisk posturograf (CDP) före och efter shuntoperation samt jämfört med HI.

Patienter och metoder.
I alla studier undersökt patienterna neurologiskt och en utvärdering av motorisk, balans och kognitiv funktion utfördes. Den motoriska funktionen utvärderades med hjälp av ett s.k. motor score (MOS) bestående av följande delar: 10 m gång på tid (sekunder) och antal, TUG på tid (sekunder) och antal steg. En ökning med 5 % eller mer ansågs signifikant. HI undersökt patienterna (n=16) och kontrollpersonerna (n=15) med MRS (absolut kvantifiering) med voxlar placerade i thalamus och i FDWM och jämfördes med varandra. I studie III och IV jämfördes patienternas (studie III, n=33; studie IV, n=35) preoperativa resultat från respektive aktigrafi och CDP med HI (studie III n=17; studie IV n=16). HI genomförde dessa undersökningar vid två tillfällen och medelvärdet beräknades. I studie II genomgick 14 patienter, och för studie III och IV vardera 20 patienter, shuntoperation och en ny MRS/aktigrafi/CDP undersökning utfördes tre månader efter operationen och jämfördes med resultaten före operation.
Resultat.
En minskning av totala N-acetyl innehållet (tNA) och N-acetylaspartat (NAA) kunde iakttas i thalamus hos patienterna jämfört med HI. Inga skillnader i ämnesomsättning kunde ses i FDWM mellan grupperna. Efter operation kunde inga skillnader i ämnesomsättning ses i thalamus, men däremot i FDWM där total cholin (tCho) ökade och myo-Inositol (mIns) minskade gränssignifikant.
Dagtid tog patienterna färre steg och hade också en lägre energiförbrukning jämfört med HI. Det förelåg ingen skillnad beträffande vilo- och sovtiden mellan patienter och HI. Efter operation förändrades vare sig antal steg, total energiförbrukning eller tid i vila/sömn jämfört med före operation.
Balansen var sämre hos patienter jämfört med HI, vilket var mer uttalat i de tester som mäter vestibulär funktion, där också antalet fall var vanligt hos patienterna. Det kunde konstateras en diskret förbättring av balansen efter operation. Ett positivt svar på shuntoperation sågs hos 86 % (studie II), 85 % (studie III) och 90 % (studie IV).

Slutsatser.
Våra resultat antyder att thalamus kan vara inblandat i patogenesen vid iNPH. I motsats till andra har vi inte funnit några förändringar av ämnesomsättningen i FDWM. Vi kunde inte finna någon ökning av vare sig tNA eller NAA i thalamus efter operation. Ökningen av tCho och den på gränsen till sänkta mIns koncentrationen skulle kunna spegla ett tillstånd av återhämtningsöket i ämnesomsättningen då tCho, en av huvudbeståndsdelarna i cellmembran, kan spegla ökad membranomsättning och sänkningen av mIns indikerar minskad glios. Den låga gångförmågan hos iNPH patienterna var förväntad men däremot var det förvånande att de inte tillbringade mer tid i vila. Ytterligare en överraskning var att patienterna inte gick mer efter operation trots att de presterade bättre på tester som mäter förmågan att gå en kort sträcka på tid vid ett givet tillfälle. Vi tror detta orsakas av vanor som är svåra att bryta och/eller avsaknad av rehabilitering.
Den uttalade nedsättningen av balansförmågan hos patienterna, särskilt i de tester som avser att mäta vestibulär funktion, antyder att det föreligger en central vestibulär störning. Den diskreta förbättringen av balansen efter operation var också oväntad sett i relation till tidigare studier.
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Am-iNPH</td>
<td>American iNPH Guidelines</td>
</tr>
<tr>
<td>$^{13}$C MRS</td>
<td>Carbon Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral Blood Flow</td>
</tr>
<tr>
<td>CDP</td>
<td>Computerised Dynamic Posturography</td>
</tr>
<tr>
<td>CDP-choline</td>
<td>Cytidine Diphosphocholine</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CSI</td>
<td>Chemical Shift Imaging</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>ELD</td>
<td>External Lumbar Drainage</td>
</tr>
<tr>
<td>Eu-iNPH</td>
<td>European multicentre study on iNPH</td>
</tr>
<tr>
<td>FDWM</td>
<td>Frontal Deep White Matter</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamate</td>
</tr>
<tr>
<td>GPi</td>
<td>Internal segment of Globus Pallidus</td>
</tr>
<tr>
<td>GPe</td>
<td>External segment of Globus Pallidus</td>
</tr>
<tr>
<td>HC</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>HI</td>
<td>Healthy Individual</td>
</tr>
<tr>
<td>$^{1}$HMRS</td>
<td>Proton Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
</tr>
<tr>
<td>iNPH</td>
<td>Idiopathic Normal Pressure Hydrocephalus</td>
</tr>
<tr>
<td>Lac</td>
<td>Lactate</td>
</tr>
<tr>
<td>LOB</td>
<td>Loss of Balance</td>
</tr>
<tr>
<td>NPH</td>
<td>Normal Pressure Hydrocephalus</td>
</tr>
<tr>
<td>mIns</td>
<td>myo-Inositol</td>
</tr>
<tr>
<td>ME-GRASE</td>
<td>MultiEcho GRadient-And-Spin Echo</td>
</tr>
<tr>
<td>MLM</td>
<td>Mixed Linear Model</td>
</tr>
</tbody>
</table>
MMSE  Mini Mental State Examination
MOS    Motor Score
MRI    Magnetic Resonance Imaging
MRS    Magnetic Resonance Spectroscopy
NAA    N-acetyl aspartate
NAAG   N-acetyl aspartate glutamate
NMR    Nuclear Magnetic Resonance
PRESS  Point Resolved Emission Spectroscopy
REML   Restricted Maximum Likelihood
R2     Relaxation Rate
RF     Radiofrequency
31 P MRS Phosphor Magnetic Resonance Spectroscopy
SOT    Sensory Organisation Test
SN     Subthalamic Nucleus
SNr    Substantia Nigra pars reticulata
T      Tesla
tCho   Total Choline
tCr    Total Creatine
tNA    Total N-acetyl compounds
TE     Echo Time
TEE    Total Energy Expenditure
TR     Repetition Time
TUGs   Timed Up and Go steps
TUGt   Timed Up and Go time
VOI    Volume of Interest
w10ms  Walk 10 metre steps
w10mt  Walk 10 metre time
INTRODUCTION

Hydrocephalus in General

Historical Overview

Congenital hydrocephalus is far more common than normal pressure hydrocephalus (NPH) (Chi, Fullerton et al. 2005) and, especially if untreated, has a distinct clinical picture, occasionally with an enormously enlarged skull making the condition easy recognisable. There are early descriptions of hydrocephalus such as those from ancient Egypt and Nubia, today’s Sudan (Armelagos 1969; Aschoff, Kremer et al. 1999).

The name hydrocephalus comes from late medical Latin, originally from the Greek words υδωρ - (hydro-) water and κεφαλη (kephalos) head. The first to use the term hydrocephalus was the encyclopaedist Celsus (1st century AD). The first detailed description of hydrocephalus was given by three Byzantine physicians, Orbasius, Aetius and Paul of Aegina in the 4-7th century AD (Lascaratos, Panourias et al. 2004).

In 1761 the Italian physician and anatomist Giovanni Battista Morgagni (1682 -1771) described three cases of adult idiopathic hydrocephalus based on pathology findings. The clinical symptoms were associated with the pathological findings much later. The Austrian paediatrician Leopold Anton Gölis (1764-1827) was the first physician to suspect that adult hydrocephalus could lead to neurological deterioration (Missori, Paolini et al. 2010). A French neurologist, Henri Roger (1881-1955), delineated the clinical picture in a 68 year-old patient in 1950 (Roger, Paillas et al. 1950) and the American psychiatrist Paul McHugh (1931- ) described three cases in 1964 (McHugh 1964).

In 1957 the Columbian neurosurgeon and inventor Salomón Hakim (1922-2011) examined a 16 year-old boy with a severe head trauma. He was semi-comatose and a pneumo-encephalogram showed enlarged ventricles but the intracranial pressure was normal. He took 15 ml CSF for laboratory testing and surprisingly the boy improved and spoke. Subsequently Hakim operated in a ventriculo-peritoneal shunt and the boy was able return to school three months later. This case and five additional ones formed the basis of Hakim’s thesis defended at the Javeriana University School of Medicine in Bogotá, Colombia in 1964 (Hakim 1964). Hakim contacted Raymond Adams (1911-2008), an American neurologist and Professor of Neuropathology at the Harvard Medical School in Boston. At first he was not interested saying “There is nothing new in this field”. Hakim met another patient and he brought him to
Boston where Adams finally became interested. This resulted in two papers published in a short time; the first in Journal of the Neurological Sciences and the second in New England Journal of Medicine, the latter with the previously skeptic Adams as first author (Adams, Fisher et al. 1965; Hakim and Adams 1965). In the papers by Hakim and Adams, six cases were presented as having a syndrome consisting of gait disturbance, urinary incontinence and prominent mental symptomatology with normal intracranial pressure (ICP) and enlarged cerebral ventricles. Of the six cases, three were secondary to trauma or cyst and three had what we today would diagnose as idiopathic Normal-Pressure Hydrocephalus (iNPH). The pioneer work by Hakim and Adams has been recognised for bringing together the symptoms, radiological appearance and improvement seen after shunt surgery.

**Classification**

Hydrocephalus (HC) is divided into non-communicating HC and communicating HC. In the former condition there is an anatomical obstruction in the cerebrospinal pathway and in the latter there is no apparent obstruction.

There are several possible sites of hindrance. There may be an obstruction in the Foramen of Monroi, usually a colloid cyst, resulting in dilatation of the lateral ventricles. If the obstruction is in the Aqueduct of Sylvius, possibly a genetically or acquired lesion, there is dilation of both lateral ventricles as well as the third ventricle. In the case of obstruction in the fourth ventricle, there will be a widening of the aqueduct as well as dilation of the lateral and third ventricles. Obstruction is also possible at the Foramina of Luschka and Magendie.

Communicating HC can be further divided; Shenkin et al. (Shenkin, Greenberg et al. 1975) introduced the term idiopathic Normal-Pressure Hydrocephalus (iNPH), where no known cause can be found, as opposed to secondary NPH where a known cause lies behind such as a subarachnoid haemorrhage, bacterial meningitis, head trauma or intracranial surgery. In both entities the ICP is within normal limits. Some patients may have subtle hydrocephalus in childhood that goes undiscovered, but at certain point in time they decompensate and develop symptomatic congenital NPH (Graff-Radford and Godersky 1989). Evidence exists that a significantly larger proportion of patients with iNPH have a larger head than expected (Wilson and Williams 2007). This subgroup is usually named arrested NPH, but also compensated NPH or LOVA (Longstanding Overt Ventriculomegaly in Adults) (Oi, Shimoda et al. 2000).
Idiopathic Normal Pressure Hydrocephalus

Epidemiology

iNPH is mainly a disease of the elderly population. Patients with arrested NPH are generally much younger when their hydrocephalus is discovered. Up to 5% of all dementias are thought to be caused by iNPH (Fisher 1982; Larson, Reifler et al. 1984). In a study by Brean et al., patients meeting the criteria for probable iNPH had a mean age of 73 years, but in the European multicentre study on iNPH (Eu-iNPH), patients without vascular risk factors were mean 70 years-old and patients with vascular risk factors 73 years-old (Brean and Eide 2008; Klinge, Hellstrom et al. 2012). No difference between male and female patients has been identified (Marmarou, Young et al. 2005; Brean and Eide 2008; Klinge, Hellstrom et al. 2012). According to the previously mentioned study by Brean et al., the prevalence of probable iNPH was 21.9/100 000 and the incidence 5.5/100 000 (Brean and Eide 2008), but much higher prevalence figures, 1.4% and 2.9%, have been found in community dwelling individuals older than 65 years in two Japanese studies (Hiraoka, Meguro et al. 2008; Tanaka, Yamaguchi et al. 2009). In Sweden the annual incidence of shunt surgery between 1996 and 1998 was 3.4 per 100 000 of whom nearly half (47%) had NPH (Tisell, Hoglund et al. 2005). In Germany the annual incidence of NPH has been reported to be 1.8 per 100 000 (Krauss and Halve 2004). The discrepancy in estimated prevalence figures and operation rates indicates a high rate of hidden cases where the reason may be lack of awareness in society and even among physicians (Conn and Lobo 2008).

Diagnosis

Under the leadership of the late Professor Anthony Marmarou (1934-2010), iNPH guidelines were developed and finally published in 2005 under the title “Guidelines for the Diagnosis and Management of idiopathic Normal-Pressure Hydrocephalus”, later named as the American iNPH-guidelines (Am-iNPH) (Marmarou, Black et al. 2005) (Table I.) This has had a great influence on diagnosis and management. Japanese guidelines were published in 2008 (Ishikawa, Hashimoto et al. 2008), but have not reached the same worldwide acceptance as the Am-iNPH. According to the Am-iNPH, a division is made between “probable”, “possible” and “unlikely” based on clinical history and findings, imaging and CSF-dynamic parameters. The main differences between the guidelines are that patients between 40 and 60 years-of age, and an ICP between 20-24.5 mmHg, cannot be diagnosed as iNPH according to the Japanese guidelines, in contrast to the Am-iNPH. Another difference is that a specific
entity “definite” iNPH is included in the Japanese guidelines requiring improvement after shunt implantation.

The value of supplemental prognostic tests is scrutinised in the Am-iNPH guidelines and the conclusion is that supplementary tests can increase the predictive accuracy of prognosis to more than 90% (Marmarou, Bergsneider et al. 2005). According to the Eu-iNPH study an improvement of 84% in the iNPH scale was reached from clinical symptoms and imaging alone (Klinge, Hellstrom et al. 2012).

**Clinical Symptoms and Signs**
In order to be diagnosed as probable iNPH a patient must have gait disturbance combined with either or both of impaired cognition and urinary disturbance (Relkin, Marmarou et al. 2005). Nearly all patients show at least discrete symptoms in all these domains as seen at the one-year follow-up in the Eu-iNPH study (Klinge, Hellstrom et al. 2012). A patient may have a severe gait problem but only subtle cognitive deficit, which is favourable in terms of successful outcome after shunt surgery (Graff-Radford, Godersky et al. 1989; Marmarou, Young et al. 2005). The opposite i.e. subtle gait problem and more profound cognitive deficit is also seen, thus the distribution of symptoms and severity can vary considerably between patients (Krauss, Faist et al. 2001). There is also great inter-individual variability concerning the severity of symptoms that may range from very discrete symptoms to being unable to walk (Hellstrom, Klinge et al. 2012). There is always an insidious onset of the symptoms as opposed to other more acute diagnoses such as cerebrovascular disease. But even if symptoms evolve slowly, there are numerous other diseases in the elderly population whose symptoms can mimic hydrocephalus or, more frequently, co-exist with iNPH (Bech-Azeddine, Waldemar et al. 2001).

There are two main ways the diagnosis is made; either after overt symptoms or, which is quite common, found accidentally when imaging the brain for other reasons.
Table I. Diagnosis according to the iNPH Guidelines (Relkin, Marmarou et al. 2005)

Probable iNPH

The diagnosis of Probable iNPH is based on clinical history, brain imaging, physical findings, and physiological criteria.

I. History

Reported symptoms should be corroborated by an informant familiar with the patient’s premorbid and current condition, and must include:

a. Insidious onset (versus acute).
b. Origin after age 40 years-of-age.
c. A minimum duration of at least 3 to 6 months.
d. No evidence of an antecedent event such as head trauma, intracerebral haemorrhage, meningitis, or other known causes of secondary hydrocephalus.
e. Progression over time.
f. No other neurological, psychiatric, or general medical conditions that are sufficient to explain the presenting symptoms.

II. Brain imaging

A brain imaging study (CT or MRI) performed after onset of symptoms must show evidence of:

a. Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evan’s index >0.3 or comparable measure).
b. No macroscopic obstruction to CSF flow.
c. At least one of the following supportive features:

1. Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy.
2. Callosal angle of 40 degrees or more.
3. Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischaemic changes or demyelination.
4. An aqueductal or fourth ventricular flow void on MRI.
III. Clinical
Findings of gait/balance disturbance must be present, plus at least one other area of impairment in cognition, urinary symptoms, or both.

With respect to gait/balance, at least two of the following should be present and not be entirely attributable to other conditions:

a. Decreased step height.
b. Decreased step length.
c. Decreased cadence (speed of walking).
d. Increased trunk sway during walking.
e. Widened standing base.
f. Toes turned outward on walking.
g. Retropulsion (spontaneous or provoked).
h. En bloc turning (turning requiring three or more steps for 180 degrees).

With respect to cognition, there must be documented impairment and/or decrease in performance on a cognitive screening instrument, or evidence of at least two of the following on examination:

a. Psychomotor slowing (increased response latency).
b. Decreased fine motor speed.
c. Decreased fine motor accuracy.
d. Difficulty dividing or maintaining attention tandem gait testing.
e. Impaired recall, especially for recent events.
f. Executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight.
g. Behavioral or personality changes.

To document symptoms in the domain of urinary continence, either one of the following should be present:

a. Episodic or persistent urinary incontinence not attributable to primary urological disorders.
b. Persistent urinary incontinence.
c. Urinary and faecal incontinence.
Or any two of the following should be present:

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

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

Possible iNPH
A diagnosis of Possible iNPH is based on historical, brain imaging, and clinical and physiological criteria.

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

II. Brain Imaging
Ventricular enlargement consistent with hydrocephalus but associated with any of the following:
a. Evidence of cerebral atrophy of sufficient severity to potentially explain ventricular size.
b. Structural lesions that may influence ventricular size.
III. Clinical
Symptoms of either:
a. Incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance.
b. Gait disturbance or dementia alone.

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

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

Gait
Difficulties in walking is often an early symptom (Fisher 1977). The typical gait is slow with reduced step length and height, involving both legs. There is a widened standing base and the toes are turned outward while walking. Problems with starting to walk and to turn around are common (Soelberg Sørensen, Jansen et al. 1986; Thompson and Marsden 1987; Stolze, Kuhtz-Buschbeck et al. 2000; Krauss, Faist et al. 2001). There is confusion about whether gait ataxia or gait apraxia is the most appropriate term to describe the gait dysfunction. Gait ataxia is mostly associated to cerebellar dysfunction, which is not the case in iNPH. Thompson advocates using the term “frontal lobe ataxia” (Thompson 2012) in favour of gait apraxia, which is defined as an impairment of gait not attributed to motor or sensory deficits. Even if no firm evidence exists, observations suggest that symptoms emanate from the frontal lobe (Thompson 2012). The sometimes preserved ability to move the legs in a recumbent position but being practically unable to walk is an interesting phenomenon that also indicates that pure motor function is not the reason for the gait difficulties. Case studies on patients suffering from symptoms caused, for example, by isolated infarction indicate bilateral involvement in the supplementary motor cortex but also the symptoms of Binswangers’s disease with
subcortical arteriosclerotic vascular changes most prominent in the frontal lobes, may give the same gait symptoms as in iNPH (Thompson and Marsden 1987; Nadeau 2007).

**Postural Function**

Unsteadiness is a frequent complaint of these patients, and a dizziness grade has been included in iNPH-severity scales (Meier 2002). Patients feel unsteady when standing and walking, and they have to use both their hands in order to get up from sitting, and they have to stand for a while before starting walking. They are often unable to stand with their legs tight together, and they fail tandem walking (Krauss, Faist et al. 2001). Soelberg-Sørensen examined patients with a force plate and could report a greater sway in iNPH patients compared to controls, and that the sway was more pronounced with their eyes closed (Soelberg Sørensen, Jansen et al. 1986). The clinical observation of a tendency to lean backwards, in contrast to the forward leaning which may be encountered in Parkinson’s disease, made Blomsterwall et al. examine postural function in iNPH. They were able to show that there is greater sway and a higher backward-directed velocity on a force platform, and that postural dysfunction is one of the symptoms that improves most after shunt operation. The postural function is also strongly associated with motor function (Blomsterwall, Bilting et al. 1995; Blomsterwall, Svantesson et al. 2000). In a test where the subject is told to place a rod in the vertical plane, those subjects with a backward movement on Romberg test showed a deviation of the subjective visual vertical, tilting the upper end of the rod towards them. This led to speculation that there might be a dysfunction in the peri-aqueductal mensencephalic region due to the dilation in hydrocephalus (Wikkelsø, Blomsterwall et al. 2003).

**Cognition**

The patients normally have some form of cognitive decline, but sometimes this is so subtle that it is not recognised by the patient, his or her relatives, or by the doctor at a brief consultation. Like gait dysfunction, the impairment in cognition is believed to be of subcortical frontal origin. Because of its easiness to handle and to evaluate, the Minimental State Examination (MMSE) (Folstein, Folstein et al. 1975) is frequently used in both studies and in the clinical setting and approximately varies between 22 and 27 (Blomsterwall, Svantesson et al. 2000; Hellstrom, Edsbagge et al. 2008; Klinge, Hellstrom et al. 2012). The MMSE, however, has well-known limitations and is influenced by age, language, education and literacy (Black, Espino et al. 1999). Some iNPH patients have severe dementia, where there is a great likelihood for other co-existing disease such as Alzheimer’s or vascular
dementia (Golomb, Wisoff et al. 2000; Bech-Azeddine, Waldemar et al. 2001). Typical symptoms are slow psychomotor speed, difficulty in maintaining attention, decreased fine motor speed, visuospatial deficits, and impaired short-term memory (Devito, Pickard et al. 2005). There are few studies on cognitive evaluation in NPH, but Iddon et al. performed a systematic examination of 11 iNPH patients before and after shunt operation and divided them into a demented and a non-demented group. The demented group showed significant recovery after surgery. The non-demented group showed impairment on tests sensitive for fronto-striatal dysfunction. This pattern was unchanged after surgery (Iddon, Pickard et al. 1999). The most ambitious attempt to study neuropsychology in iNPH was made by Hellström et al, who performed a large battery of neuropsychological tests measuring vigilance, fine movements of the hand, learning, working memory and aspects on executive functions, on 58 iNPH patients and compared the results with 108 healthy individuals. They found that all tests were performed worse in the patient group (Hellstrom, Edsbagge et al. 2007) and that there was a significant improvement in most of the tests after shunt surgery (Hellstrom, Edsbagge et al. 2008).

Micturition

Urgency to micturate in iNPH is one of the originally described symptoms, but one not so well studied. Some efforts, however, have been made to characterise these difficulties. Jonas et al. performed cystometry on 5 patients with iNPH and found a neurogenic disturbance (Jonas and Brown 1975). Ahlberg et al performed urodynamic tests in four patients with NPH, one with Alzheimer’s disease and five with multi-infarct dementia. The hyperdynamic bladder activity could be temporarily improved by a lumbar tap test and later abolished after shunt surgery (Ahlberg, Norlen et al. 1988). In a retrospective study on 42 patients who underwent urodynamometry before shunt surgery, 93 % had lower urinary tract symptoms. The majority had storage symptoms such as urgency, frequent nocturnal urination, and incontinence. Seventy-one per cent had voiding symptoms such as difficulties in initiating urination, poor flow, etc. (Sakakibara, Kanda et al. 2008). The same group also found a correlation between right frontal hypoperfusion in the brain and urinary dysfunction in iNPH (Sakakibara, Uchida et al. 2012). Urgency to micturate is usually not the first symptom and it is not always present. Urgency sometimes develops into urine incontinence and in severe cases may also involve difficulty in faeces control, the latter being even less studied than urgency to micturate, and no single study addressing this problem can be found even though it is occasionally encountered clinically and is also mentioned in the Am-iNPH guidelines.
**Imaging in Clinical Practice**

**Computed Tomography**
In normal clinical practice, computed tomography (CT) of the brain is used as a radiological screening method for diagnosing NPH. Radiological appearances that have been found to favour the diagnosis of NPH are: a symmetrical widening of the ventricular system most pronounced in the frontal and temporal horns with an Evans ratio > 0.3; a flattening of the high convexity gyri (Tans 1979); and an enlarged third ventricle (Wikkelsø, Andersson et al. 1986).

**Magnetic Resonance Imaging**
MRI is the method of choice due to higher resolution and lack of sensitivity of CSF dynamics in CT. Sagittal T1 and T2 is the best way to find pathology in the Aqueduct of Sylvius (Figure 1.1). It is also possible to visualise hyperdynamic flow in the aqueduct (flow-void) using phase contrast cine MRI. If a flow void can be observed it is a sign of an open aqueduct. The flow-void is reported to be related to favourable outcome in some studies (Bradley, Whittemore et al. 1991; Bradley, Scalzo et al. 1996) whereas others have not been able to reproduce this finding (Krauss and Regel 1997; Hakim and Black 1998). Coronal T2 sequences allow imaging of the lateral ventricles, especially the temporal horns (Figure 1.2). Axial (or transversal) T2 sequences (Figure 1.3) with FLAIR are suitable for studying changes in fluid, i.e. oedema but also vascular depth with matter hyperintensities frequently seen in iNPH correlating to the severity of symptoms, but does not predict a poor response to shunt surgery (Tullberg, Jensen et al. 2001). On the contrary, they have the same rates of improvement as those patients without high vascular load. (Hellstrom, Edsbagge et al. 2008; Klinge, Hellstrom et al. 2012). In the Am-iNPH guidelines it is stated that a callosal angle of 40° or more supports the diagnosis of probable iNPH but no reference is given. The callosal angle varies depending on which plane it is measured from. Ishii et al. defined that it should be measured on the coronal plane just on the posterior commissure. In comparison with HI and Alzheimer patients the callosal angle in iNPH patients was significantly smaller, 66° versus 104° and 112° for the Alzheimer patients and HI respectively (Ishii, Kanda et al. 2008).
**Figure 1.** MRI from an iNPH patient (1.1): Sagittal T2 showing a flow void sign indicating an open aqueduct; (1.2): coronal T1, (1.3): Axial T2.
Volumetry

Being able to measure the volume of the CSF system more accurately would increase the diagnostic validity of iNPH. A reduction in the volume of CSF is also compatible with a working shunt, but there is also evidence that a decreased volume is not mandatory for improvement (Meier, Paris et al. 2003). One possibility, however, is that our instruments have been to blunt to measure decreases in CSF volume. Volumetry is an imaging technique that measures the intraventricular volume instead of the less accurate Evan’s ratio (distance between frontal horns divided by the maximum inner diameter of the skull) (Evans 1942). Until now volumetry has been time-consuming due to manual quantification, but automatic measurements have now been introduced that are faster and reliable (Lemieux, Hammers et al. 2003; Ambarki, Lindqvist et al. 2012).
Methods for Assessing CSF Dynamics

CSF Infusion Tests
Katzman & Hussey presented the constant-infusion lumbar infusion test in 1970, aimed at measuring the CSF-outflow resistance (Katzman and Hussey 1970). Czosnyka et al. developed a computerised version (Czosnyka, Batorski et al. 1990). Marmarou introduced the bolus injection of fluid into the CSF, which is the quickest and least invasive method, but probably not as accurate as the above-mentioned tests (Marmarou, Shulman et al. 1975). Yet another method of assessing CSF dynamics, named constant pressure method was described by Ekstedt (Ekstedt 1977). A description and a comparison of the available methods for assessing CSF dynamics have been presented in a review article by Eklund et al. (Eklund, Smielewski et al. 2007). Infusion tests, apart from estimating the outflow resistance, also provide valuable information about compliance and CSF production rate. The use of CSF outflow resistance (or the reciprocal outflow conductance) when selecting patients for shunt surgery has not yet been established, since diverging predictive values have been reported (Borgesen and Gjerris 1982; Tans and Poortvliet 1984; Malm, Kristensen et al. 1995; Delwel, de Jong et al. 2005). Reference values for CSF outflow resistance in 40 elderly subjects were found to be 8.6 mmHg/mL/min. and the 90th percentile was 17.4 mm Hg/mL/min (Malm, Jacobsson et al. 2011).

Intracranial Pressure Measurements
There is general agreement on the upper limits of ICP measured via lumbar puncture with the patient resting in a recumbent position. It should not exceed 18 mm Hg/24.5 cm H₂O/2.4 kPa. The Am-iNPH guidelines suggest 5 mm Hg to be the lower limit, while there is no lower limit mentioned in the Eu-iNPH study (Relkin, Marmarou et al. 2005; Klinge, Hellstrom et al. 2012). Pressure is said to be “normal” but this is not exactly true, because ICP in iNPH has been shown to be slightly higher compared to controls, though within normal limits (Malm, Kristensen et al. 1995). Reference ICP values gain from for 40 healthy elderly were 11.6 mm Hg and the reference interval was 7.8-14.3 mm Hg (Malm, Jacobsson et al. 2011).

The presence of slow rhythmic oscillations (B-waves) > 50% of registration time has been argued to be the best predictor of a shunt response (Graff-Radford, Godersky et al. 1989) but Stephensen et al. found only a weak correlation with the postoperative result (Stephensen, Andersson et al. 2005).
Eide developed a method for analysing intracranial pulse pressure amplitudes which he claimed is able to distinguish between iNPH patients who respond to a shunt operation and those who do not respond (Eide 2006; Eide 2006).

**CSF Tap Test**

CSF tap test where 50 ml CSF is removed was introduced by Wikkelsø (Wikkelsø, Andersson et al. 1986). Clinical baseline parameters are measured before and after and the percentage change is estimated. The strength is that it is easy, safe and has a high positive predictive value, but its weakness is a considerably lower negative predictive value (Kahlon, Sundbarg et al. 2002). Another weakness is that this test has never been submitted to a placebo-controlled test. At least one ongoing study concerning this issue will hopefully bring clarification on the magnitude of the placebo effect in the CSF tap test.

**External Lumbar Drainage**

To overcome the weakness of the CSF tap test, Marmarou developed an external drainage test (ELD) where the patient has a lumbar drain for 3 days. This provides a higher sensitivity but the disadvantage is that is more invasive with an increased risk for CSF infection (Marmarou, Bergsneider et al. 2005).

**CSF Biochemical Analysis**

Biochemical analysis of CSF is important for differentiating between idiopathic and secondary NPH in clinical practice. An elevated leucocyte count, signs of intrathecal antibody production, increased albumin, and the presence of antibodies against Borrelia burgdorferi are compatible with a secondary cause. Other CSF markers do not have the same diagnostic value but may indicate other pathology such as Alzheimer’s disease. Generally, however, these markers are not sensitive and specific enough to be included in the diagnostic work-up (Tarnaris, Toma et al. 2009).

Increased neurofilament protein, believed to be a sign of axonal dysfunction, has been found in several studies (Tullberg, Rosengren et al. 1998; Agren-Wilsson, Lekman et al. 2007; Tullberg, Blennow et al. 2007). Elevated levels of glial fibrillary acidic protein indicating astrogliosis have also been found (Albrechtsen, Sorensen et al. 1985; Tullberg, Rosengren et al. 1998). Elevated TNFα has been reported and interpreted as a sign of an inflammatory state (Tarkowski, Tullberg et al. 2003). Various results have been reported for tau-protein and β-amyloid_1-42_. Ägren-Wilsson found a decreased T-tau, P tau and β-amyloid_1-42_ in iNPH compared to controls (Agren-Wilsson, Lekman et al. 2007) but also increased (Kudo, Mima et
al. 2000; Kapaki, Paraskevas et al. 2007) and normal tau have also been reported (Zemlan, Rosenberg et al. 1999). In a recent paper p-tau and soluble amyloid precursor protein α were found to be strong diagnostic markers when distinguishing between iNPH, Alzheimer’s disease and controls (Miyajima, Nakajima et al. 2012).

**Pathophysiology**

Our understanding of the pathophysiological mechanisms involved in the development of iNPH is still insufficient, but several factors are believed to be of importance. The principal alternatives explaining the neuronal dysfunction are: mechanical stretching; parenchymal oedema with deranged metabolic function; and a defect in clearance of toxic products caused either by diminished blood flow in the periventricular area or reduced CSF turnover.

Initially there is impaired absorption of CSF through the arachnoidal villi into the venous blood (Borgesen 1984) resulting in a higher CSF-pressure. Compensatory ventricular enlargement (Hakim and Adams 1965) and possibly increased CSF absorption in the periventricular white matter (Deo-Narine, Gomez et al. 1994) lead to a new steady state causing the pressure to decrease to normal levels. Another theory is that ventriculomegaly is caused by increased intracranial pressure pulse amplitude, the so called water-hammer effect (Di Rocco, Di Trapani et al. 1979).

It is well-known that patients with iNPH have a higher incidence of cerebrovascular disease (Krauss, Droste et al. 1996) and there is an association between high ICP and impaired cerebrovascular autoregulation (Haubrich, Czosnyka et al. 2007). On MRI there are increased vascular white matter changes (Tullberg, Hultin et al. 2002), and histologically microvascular infarctions but also interstitial oedema, ependymal disruption, gliosis and neuronal degeneration have been found (Akai, Uchigasaki et al. 1987; Del Bigio 1993).

As well as co-existing vascular changes in iNPH, there is also an increased incidence of pathological changes seen in Alzheimer’s disease (Bech, Waldemar et al. 1999; Savolainen, Paljarvi et al. 1999; Golomb, Wisoff et al. 2000). This has led to speculations that a decrease in CSF turnover may lead to accumulation of neurotoxic substances (Silverberg, Mayo et al. 2003) and attempts have been made to shunt patients with Alzheimer’s (Silverberg, Mayo et al. 2008).

Cerebral blood flow (CBF) studies in iNPH have consistently shown global and frontal hypoperfusion (Owler and Pickard 2001). CBF has been found to be decreased and to
correlate with CSF pressure in the basal ganglia and the thalamus (Owler, Momjian et al. 2004) and in the periventricular white matter (Momjian, Owler et al. 2004). Microdialysis in iNPH patients (Agren-Wilsson, Roslin et al. 2003) and presence of lactate in animal MRS models (Braun, Dijkhuizen et al. 1997; Braun, van Eijdsen et al. 1999) have indicated a state of chronic ischaemia but lactate has not been found in human MRS (Braun, Gooskens et al. 2003; Lenfeldt, Hauksson et al. 2008). This may be due to animal models not being sufficiently good to simulate human hydrocephalus. Other possibilities include methodological differences and that there might be subsets of patients with elevated lactate i.e. patients with considerable vascular disease in iNPH (Kondziella, Sonnewald et al. 2008).

Yakovlev described the somatotopic organisation of corticospinal tract neurons in the vicinity of the lateral ventricles, with neurons serving the arms and face placed more medially than those serving the legs. This gave a clinical picture of spastic diplegia in patients with congenital hydrocephalus (Yakovlev 1947) as was also previously believed to apply to NPH. Sudarsky and Simon performed a computerised gait analysis with electromyography (EMG) in hydrocephalic patients showing co-contraction in the antagonist muscles (Sudarsky and Simon 1987). In a study by Zaaroor et al. on motor-evoked potentials, there was no significant difference between patients and controls, and the potentials did not change after shunt surgery (Zaaroor, Bleich et al. 1997). These results and the clinical resemblance to Parkinson-like syndromes indicate that subcortical structures and/or basal ganglia and/or the thalamus may be involved in the pathogenesis. The flow of information through the basal ganglia is topographically organised from the cortex through the basal ganglia to the thalamus and back to the cortex. Although iNPH patients do not have dysfunction in the pyramidal tract, the somatotopic description by Yakolev is interesting in the understanding of the distribution of the more pronounced symptoms in the legs compared to the arms. The thalamus is certainly of great interest in iNPH both because of its localisation close to the third ventricle, and because of neurophysiological and anatomical considerations; the thalamus is not only involved in motor but also many cognitive processes (Haber and Calzavara 2009). Connections exist between the frontal cortex and the thalamus. Within the basal ganglia there are output pathways to the thalamus; a direct pathway from the striatum to the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulate (SNr), and an indirect pathway from the external segment of the globus pallidus (GPe) to the subthalamic nucleus (SN), from the SN to the GPi, and from the GPi to the thalamus. Projections from the striatum to both the direct and indirect pathways are GABA-ergic and inhibitory. Projections from the globus
pallidus/substantia nigra are also GABA-ergic and inhibitory. Activation of the direct pathway results in disinhibition of the thalamus. The SN sends excitatory inputs to the GPi. Thus the direct and indirect pathways have opposing effects (Haber and McFarland 2001) (Figure 2). In conclusion, neuroanatomical considerations, clinical observations, neurophysiological data, CBF-studies in combination with CSF-dynamics, microdialysis and MRS indicate a disturbance of the cortico-basal ganglia-thalamocortical circuit in iNPH.

Figure 2. A schematic presentation of the cortico-basal ganglia-thalamocortical circuit. Excitatory input comes from the cortex to the striatum and from the striatum inhibitory impulses go to both GPi/SN (direct pathway, black) and the GPe (indirect pathway, grey). Inhibitory impulses are sent from the GPe to the STN, which sends excitatory output to the GPi. GPi=Globus Pallidus Interna, GPe=Globus Pallidus Externa, SN=Substantia Nigra, STN=Subthalamic Nucleus.
**Treatment**

At present the only effective well-established treatment is a shunt (Figure 3), but due to lack of Level 1 evidence, a Cochrane review from 2001 stated “There is no evidence to indicate whether placement of a shunt is effective in the management of NPH” (Esmonde and Cooke 2003). Since then a double-blind randomised controlled study on patients with iNPH and severe vascular load has shown that shunt surgery is effective (Tisell, Tullberg et al. 2011), and there is also an on-going study with the intention of providing Level 1 evidence that shunt surgery is effective (Toma, Papadopoulos et al. 2012).

In the retrospective Italian Multicenter study on endoscopic third ventriculostomy (ETV) in iNPH 110 cases were reviewed and outcome assessed two years after the operation. A clinical improvement rate was reported in 69.1 % and it seems to offer a promising alternative future treatment but further studies with a prospective design are warranted before any conclusion can be drawn whether ETV is effective and safe in iNPH or not (Gangemi, Maiuri et al. 2008).

Pharmacological treatment has also been tried with, for instance, acetazolamide, a carbonanhydrase inhibitor resulting in a decreased production of CSF, where some success has been reported in one French study (Aimard, Vighetto et al. 1990) but this has not gained any further interest.

The gold standard procedure, however, is the diversion of the cerebrospinal fluid via a shunt containing a valve that opens at a certain pressure allowing CSF to be drained from the ventricular system to the peritoneum or, less commonly, to the right atrium of the heart. The least common form of drainage is from the lumbar CSF space to the peritoneum (Patwardhan and Nanda 2005). There exists a plethora of shunts from several manufacturers. Early shunts had a valve with fixed opening pressure but nowadays it is more common to use so-called programmable or adjustable shunts where the opening pressure can easily be changed without surgical intervention so as to avoid under- and overdrainage. In case of a subdural haematoma the pressure may be set at a higher opening pressure, thus possibly avoiding surgical evacuation. If improvement has not reached the expected level and underdrainage is suspected, setting a lower opening pressure may improve the outcome as shown in a retrospective study (Zemack and Romner 2002), but until now no prospective study confirming these results has been published. Overdrainage in the erect position may occasionally cause problems with subdural haematoma and headache. To avoid this, an anti-siphon device exists that acts through increasing flow resistance in the erect position, thus reducing CSF loss.
Outcome with or without Shunt Surgery

No definite consensus on how and when to best assess the effect of shunt surgery has been published. This makes comparison between studies difficult, sometimes impossible. Some researchers have evaluated outcome using functional grading (Stein and Langfitt 1974; Black 1980) while others have applied a more precise approach rating the degree of change in gait, cognition and urination (Krauss, Droste et al. 1996; Boon, Tans et al. 1997). Others have included exact measurements of gait and cognition prospectively (Larsson, Wikkelso et al. 1991; Malm, Kristensen et al. 1995; Savolainen, Hurskainen et al. 2002). In a systematic review by Hebb et al. where data from a large number of studies, having an objective system for the functional grading of patients pre- and postoperatively, were scrutinised showing an average 59% (24-100) short-term positive response to shunt surgery. Long-term positive response was much lower; 29 % (10-100) (Hebb and Cusimano 2001). More recent studies involving relatively large number of patients have shown considerably higher figures, 80-90 % (Klinge, Hellstrom et al. 2012; Poca, Solana et al. 2012). An attempt to introduce a calibrated and norm-based scale containing several continuous variables to describe the
severity of illness and evaluation of changes after treatment has recently been published. The scale contains four domains, namely gait, neuropsychology, balance and urinary continence (Hellstrom, Klinge et al. 2012).

A general drawback with the current methods of testing is that it may not answer the question whether or not the improvement seen at a point in time really reflects functional improvement in the patient’s everyday life.

The natural history of iNPH has not been studied well. In a recent literature search performed by Toma et al. only seven studies including 102 patients could be identified fulfilling the criterion; an objective description of outcome without shunt insertion, and only one study was designed to compare the outcome of shunt versus no shunt. Despite rather weak evidence, the authors concluded that a measurable deterioration at three months could be found in most patients without shunt (Toma, Stapleton et al. 2011).

**Shunt Complications**

Shunt complication is a frequent dilemma but serious adverse advents occur relatively infrequently. According to Hebb et al. the pooled mean complication rate was 38% (5-100) and the complications reported (in order of frequency) were: subdural effusion/haematomas, mechanical malfunction, cerebrovascular incident, infections and seizures (Hebb and Cusimano 2001). In the Eu-iNPH study, 28% of the patients experienced complications, 13% treated conservatively and 15% surgically (Klinge, Hellstrom et al. 2012), whereas another recent prospective study of 236 patients showed less than 12% early and late shunt complications with a 0.8% mortality rate (Poca, Solana et al. 2012).
**Magnetic Resonance Spectroscopy**

The brain may be studied morphologically with magnetic resonance imaging (MRI) and its metabolism may be studied with magnetic resonance spectroscopy (MRS). The difference is that MRI uses high spatial resolution to create images, whereas MRS uses spectroscopy to give information on the chemical status of the tissue. The basis for this is the dependency of the resonance frequency of a nucleus on its environment. It is possible to separate molecules from each other in an MR spectrum because of their peak position. This allows quantitative non-invasive evaluation of the concentrations of several metabolites in the brain. Three nuclei may be used for spectroscopy, $^1$H, $^{31}$P, and $^{13}$C, each providing different spectra. $^{31}$P MRS gives information about high-energy phosphate metabolism and membrane phospholipid metabolism. MR sensitivity for phosphor, however, is low compared to protons requiring a larger voxel for accurate signal-to-noise ratios. $^{13}$C MRS can provide information about lactate production and turnover, for instance, but has still to be developed before being suitable for use in studies on hydrocephalus (Braun, Vandertop et al. 2000).

The volume examined where the voxel is placed is called the Volume of Interest (VOI). Two techniques are generally used, single voxel and multi-voxel, the latter also named chemical shift imaging (CSI). When using single voxel, two techniques are used for three-dimensional spatial localisation; PRESS (Point REsolved SpectroScopy) or STEAM (STimulated Echo Acquisition Mode).

The most commonly used nucleus is $^1$H. A typical MRS spectrum (Figure 4.) contains peaks of total N-acetyl compounds (tNA) consisting of the sum of N-acetyl aspartate (NAA) which is most abundant, and a minor part N-acetyl aspartate glutamate (NAAG). NAA is produced in the mitochondriae of the neuron and is regarded a marker of neuronal density, though the exact role is unknown (Soares and Law 2009). NAAG has been suggested to be involved in excitatory transmission and a source of glutamate (Coyle 1997). Total creatine (tCr) consisting of the sum of phosphor-creatine and creatine is a marker of energy deposits (Govindaraju, Young et al. 2000). It has previously been believed to be stable and has therefore been used as a concentration reference, though this has been seriously questioned (Li, Wang et al. 2003). Total choline (tCho) consists of free choline, glycerolphosphorylcholine and phosphoryl-choline. Choline is required for synthesis of the neurotransmitter acetylcholine and for phosphatidylcholine, which is essential for the cell membrane. Since the concentration of free choline is small, tCho is thought to represent membrane turnover (Govindaraju, Young et al. 2000). There is evidence that myo-Inositol (mIns) is involved in
cell growth (Ross 1991) and it has also been proposed as a glia cell marker (Brand, Richter-Landsberg et al. 1993). Glutamate (Glu) is the most abundant amino acid in the brain and its main role is an excitatory neurotransmitter (Ross 1991). Lactate (Lac) is the final product of anaerobic glycolysis and under normal circumstances it is not present in the brain. In states of compromised circulation such as stroke, trauma and seizures it may increase considerably (Rudkin and Arnold 1999).

![MRS spectrum](image)

**Figure 4.** Example of an MRS spectrum from FDWM in a HI. The main peaks NAA, Cr, Cho and mIns are shown.

### Absolute Quantification

Metabolite concentrations are often expressed as ratios, most frequently with creatine as the denominator. This may sometimes be sufficient, but a more elaborate superior method is absolute quantification. The reason for this is that the concentration of creatine is not stable and is influenced by systemic conditions such as renal disease or an inborn error of creatine
metabolism, the latter, though, being a rarity, and this may obscure the results (Soares and Law 2009). Pathology in the brain such as glioma also is associated with reduced creatine concentrations (Lowry, Berger et al. 1977). Evidence exists that the coefficient of variance is lower for absolute concentrations than for ratios (Schirmer and Auer 2000; Li, Wang et al. 2003). An uncertain denominator causes error and may give rise to invalid conclusions.

**Magnetic Resonance Spectroscopy in NPH**

There are only a few published studies on MRS in patients with hydrocephalus, the first reports published in the beginning of the 1990’s. In these reports NPH is only one of several pathologies studied (Hugg, Matson et al. 1992; Ross, Kreis et al. 1992; Shiino, Matsuda et al. 1993).

In a study by Kizu et al. proton CSI was used in 9 patients with NPH and compared with 6 patients with other types of dementia (Alzheimer and Pick) and 5 control subjects. Lactate was found in the lateral ventricle of all NPH patients but not in the dementia or control subjects (Kizu, Yamada et al. 2001).

In 2003 Braun et al. published a report on 24 patients with hydrocephalus and among these, five were diagnosed as iNPH. $^1$H-MRS was used and the voxels were positioned in the periventricular white matter. No metabolic abnormalities could be detected (Braun, Gooskens et al. 2003). One possible reason why there were no significant differences might be the very heterogeneous patient sample.

Shiino et al. examined 21 patients with secondary NPH before and after shunt operation using $^1$H-MRS with a voxel in the periventricular white matter. Significant preoperative differences in NAA/Cr and NAA/Cho were seen between patients with excellent and poor outcome but there were no changes pre- versus postoperatively (Shiino, Nishida et al. 2004).

In recent years three studies on iNPH patients using $^1$H-MRS have been performed. Del Mar Matarin et al. in a study on 12 patients, placed the voxels in the medial frontal lobes covering the anterior cingulate cortex of both hemispheres, before and after shunt surgery. Following surgery there was an increase in NAA/Cr and NAA/Cho and decreases in mIns/Cr and Cho/Cr (del Mar Matarin, Pueyo et al. 2007).

Lenfeldt et al. studied 18 iNPH patients before and after external lumbar drainage (ELD). A very large voxel was placed in the frontal white matter. The result was a lower NAA/Cr ratio in patients than in controls but no difference in the Cho/Cr ratio. Patients that improved had higher NAA/Cr ratios than patients that did not improve (Lenfeldt, Hauksson et al. 2008).
Finally Algin et al. studied 18 iNPH patients, 11 patients with other forms of dementia, and 20 controls. A large voxel situated in the frontal lobe was used. Patients with iNPH and other dementias had significantly lower NAA/Cho ratios than controls. The iNPH group also had a lower NAA/Cr ratio than the controls (Algin, Hakyemez et al. 2010). A weakness of this study was that the controls were younger than the patients, which may have influenced the result.
**Actigraphy**

Actigraphy is a method involving computerised monitoring and collection of data from humans at rest and activity by the detection of movements. It has been used for many years in the field of medicine, particularly in the study of sleep. With technological advances in recent years it has become a useful and valid research instrument. The sensor is usually worn on the wrist or the upper arm (Figure 5.), but may also be worn on the leg. A so-called piezo-electric beam detects movements in two or three axes which are then converted to digital counts in a predefined period of time (e.g. 1 min); an epoch. The actigraph has the advantage of being able to be used for several days or even weeks in nearly all environments apart from water. Data are downloaded to a computer when the monitoring process has been completed (Sadeh 2011) (Figure 6.). There is a wide variety of actigraphs with different algorithms based on movement detection in different axes, together with heat flux sensor, skin temperature sensor and galvanic skin response to calculate steps, energy consumption, time spent lying and standing and during sleep.

SenseWear actigraphy (BodyMedia Inc., Pittsburgh, PA, USA) is widely used and has been validated for exploring activity and rest in healthy young individuals (Fruin and Rankin 2004; St-Onge, Mignault et al. 2007) as well as older healthy persons (Heiermann, Khalaj Hedayati et al. 2011; Mackey, Manini et al. 2011). It has also been used in clinical medicine to assess patient activity (Hill, Dolmage et al. 2010; Almeida, Wasko et al. 2011; Avesani, Kamimura et al. 2011).

Though this method has never been used in patients with iNPH before, it is well suited for an analysis of a change in basal parameters such as ambulatory activity and sleep/rest periods in a subject’s everyday life after intervention.
Figure 5. SenseWear armband.

Figure 6. Presentation of data from SenseWear, showing recordings from Saturday to Thursday for total energy expenditure (TEE). (Published with permission from ResMed Sweden)
Computerised Dynamic Posturography

Maintaining balance is a very complex central integration of vision, proprioception, muscle activation and vestibular function. In elderly people balance impairment, and its feared consequence falling, has a huge impact on morbidity and premature death (Rubenstein 2006) and for society the costs are enormous (Church, Goodall et al. 2011). Clinical testing of balance is often performed using Romberg’s test, tandem walking or standing on one leg. Balance scales have been developed such as the Tinetti Balance and Gait test (Tinetti, Williams et al. 1986) and the Berg Functional Balance Scale (Berg and Norman 1996). These are basically easy to use but they have a ceiling effect, which means that even those with rather poor balance may manage the test (Mancini and Horak 2010). A low score may not even reflect poor balance but rather lack of motivation, cognitive dysfunction or pain. Instrumental methods have been developed for assessing balance more accurately.

Computerised Dynamic Posturography (CDP) can objectively measure a subject’s three sensory inputs, namely vision, proprioception and vestibular function at the same time. The method is based on measurement of ground reaction forces from which the centre of pressure and sway may be calculated (Chaudhry, Bukiet et al. 2011). These sensory inputs are integrated and interpreted in central vestibular areas in the brain stem; subsequently descending neuronal pathways to the muscles are activated in order to maintain balance (Visser, Carpenter et al. 2008). There are several instruments available for assessing postural control. The simplest equipment is a force plate. A more advanced method is the Equitest (Figure 7.), which is one of the best studied (Black 2001). It is based on the Sensory Organisation Test (SOT) which objectively identifies problems with postural control by assessing the patient's ability to make effective use of (or suppress inappropriate) visual, vestibular, and proprioceptive information (Nashner and Peters 1990) and is presented as scores from 0-100 where 100 is no sway and best possible balance, and 0 is equal to falling (Figure 8.).

Equitest has never been used to study patients with iNPH before, but different kinds of force platform have been used in earlier studies (Soelberg Sørensen, Jansen et al. 1986; Blomsterwall, Svantesson et al. 2000; Czerwosz, Szczepak et al. 2008; Czerwosz, Szczepak et al. 2009).
Figure 7. The Equitest equipment.
(Image courtesy of Natus Medical Inc.)

Figure 8. Example of protocol for Sensory Organizing Test (SOT)
1-6 and composite. Score 0-100. N/S= No Score
AIMS OF THIS THESIS

I. To demonstrate that there was a reduced metabolism in the thalamus and the FDWM in iNPH patients in comparison with HI.

II. Primarily to investigate if the improvement of symptoms by a shunt operation would move tNA and NAA towards normalisation in the thalamus, and secondly, if there were any other metabolic changes either in the thalamus or in the FDWM postoperatively.

III. To measure motor function, energy expenditure and resting/sleeping time in iNPH patients before and after shunt surgery, in comparison with HI, by actigraphy in order to characterise the impact of the impairment on everyday life and also possible improvements after surgery.

IV. To describe the postural function in iNPH patients by CDP pre-and post-operatively in comparison with HI.
SUBJECTS AND METHODS

All patients referred to the Department of Neurology, University Hospital, Linköping from the South-eastern Region of Sweden between 2007 and 2010 fulfilling the criteria for probable iNPH criteria according to the Am-iNPH guidelines, slightly modified, were consecutively included. In Studies I and II the modification was that MMSE should be between 21 and 30. Clinically they were required to have gait disturbance in both legs unexplained by other conditions, disturbance of tandem walking, multistep turning, small steps and wide-based gait. Bladder dysfunction and or cognitive impairment could be present. Cortical symptoms such as aphasia, apraxia or agnosia were not accepted. Radiologically: symmetrical communicating ventricular enlargement without cortical infarcts or other lesions of clinical importance apart from lacunar infarcts (< 1cc); an Evans index ≥ 0.3; the temporal horns and third ventricle should be relatively enlarged. Mild to moderate cortical atrophy and subcortical white matter hyperintensities were allowed.

In all four studies an ICP higher than 18 mm Hg (24.5 cm H2O or 2.4 kPa), CSF changes indicating a secondary aetiology of NPH, non-cooperative patient, and short expected survival time were all exclusion criteria.

For Studies I and II, more specifically, patients with infarction in the thalamus and in the frontal lobes were excluded.

The HI serving as controls in this material were mainly recruited from friends and relatives of hospital staff. They considered themselves healthy and without any obvious gait or cognitive deficit, which was confirmed at examination. Previous disease not impairing gait and ongoing medication were not reasons for exclusion.

Patients and Healthy Individuals
(Table II-III)

In Study I 20 consecutive patients, 12 males and 8 females with a mean age 74 (49-83) years were consecutively recruited and included. Four of the 20 patients were excluded from the study. The reasons for this were neuroborreliosis (1), severe heart failure (1), not willing to participate (1) and MMSE < 21 (1). Sixteen patients, 9 males and 7 females aged 74 (49-83) were finally included in the study.
Table II  iNPH patients in Studies I IV

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46
In Study II 19 consecutive patients, 11 males and 8 females, mean age 75 (49-83) years were recruited and included in the study. Of the 19 patients included, 3 males and 2 females were excluded from the study due to shunt dysfunction (3), a subdural haematoma (1), and an infarction in the frontal lobe (1) between the operation and the three-month follow-up. The remaining 14 patients aged 74 (49-83) were included in the analysis.

In Studies I and II 16 healthy elderly people, 7 males and 9 females, mean age 73 (62-89) years, served as controls. One of the 16 HI was excluded as the MRS examination was lost due to data error. Thus fifteen remained in the study. Because of lacunar infarctions in the thalamus in one HI the voxels in the thalamus were excluded.

In Study III there were 33 consecutive patients, 17 males and 16 females, with a mean age of 73 years (range 49-81). Thirteen patients never underwent a second actigraphy recording. The reasons for this were: subdural haematoma (2) epidural/subdural haematoma postoperatively (2), and an intracerebral perioperative haematoma (1). Three (3) patients developed shunt dysfunction. There was also one (1) incomplete recording and one (1) patient was excluded due to severe back pain. Finally, three (3) patients never had surgery; one declined surgery, one had a negative preoperative examination and the third violated the protocol.

In this study, 17 HI, 8 males and 9 females with a mean age of 73 years (range 62-89) were controls. One individual experienced technical problems during the second recording session.

In Study IV, 35 patients, 16 males, 19 females, with mean age of 73 (49-81) were included. Twenty patients were evaluated preoperatively and three months postoperatively. Reasons for not being evaluated postoperatively were: five (5) haematomas (subdural, epidural/subdural and intracerebral) postoperatively; three (3) shunt dysfunctions (two proximal and one distal); three (3) patients refused either surgery (one) or a second posturography (two); three (3) were not evaluated a second time due to logistic reasons; and one (1) had a negative external lumbar drainage test and was not operated.

Sixteen HI, 7 males, 9 females aged 73 (62-89) were consecutively recruited as controls.

In table II and III an overview of all participating patients and HI in Study I-IV are shown.

**Ethical Approval**

Written consent was obtained from all patients and HI. The studies were conducted according to the Declaration of Helsinki. Ethical approval for the studies was obtained from the Local Ethics Committee (Dnr M11-07).
**Clinical Assessment**

In all four studies the patients underwent a structured neurological examination by a neurologist (FL) in the outpatient clinic, and later an MRI of the brain was performed. Motor function was examined by a physiotherapist and included time for 10 metre walk in seconds (w10mt), and number of steps (w10ms) at a self-selected speed with their usual walking aid were registered, Timed Up and Go test (Blomsterwall, Svantesson et al. 2000) in seconds and steps (TUGt, TUGs) (Mathias, Nayak et al. 1986). The Gait Test was performed in all studies, though only reported in Study I, according to the following: 1, normal; 2, insecure; 3, insecure with cane; 4, bi-manual support; 5, aided; 6, wheelchair (Larsson, Wikkelso et al. 1991). The balance test used was Romberg’s, slightly modified from Blomsterwall et al. (Blomsterwall, Svantesson et al. 2000), and it was performed standing, with the feet together, eyes closed and hands on the chest. Time in seconds to correction up to 60 seconds was registered. An occupational therapist performed the MMSE test (Folstein, Folstein et al. 1975). Lumbar CSF pressure was measured either manually in the recumbent position or automatically if a computerised lumbar infusion study was performed. Lumbar CSF pressure was measured and samples for cells and proteins were analysed to exclude patients with secondary normal-pressure hydrocephalus.

The HI were examined by a neurologist (FL), including 10 meter walking test (measured in seconds), number of steps, and Romberg’s test. MMSE was performed for cognitive function.

**Shunt Surgery**

Patients received a ventriculo-peritoneal shunt, in the vast majority a programmable Codman-Hakim (Codman/Johnson & Johnson, Raynham, MA) but in some cases a fixed pressure valve Codman- Hakim (Codman/Johnson & Johnson, Raynham, MA) medium-high, was used, in Study II (n=2), Study III (n=1) and in Study IV (n=3). The opening pressure of the shunt was set at mean 110 (60-150) mm H2O.

**Postoperative Evaluation**

The patients were examined three months postoperatively and significant improvement was defined as a 5% improvement in motor score (MOS). MOS was calculated as a composite score, with the percentage change of each item expressed as follows: \((\Delta w10mt+\Delta w10ms+\Delta TUGt+\Delta TUGs)/4\). When the patients improved 5 % the shunt was considered to be successful.
Shunt dysfunction was considered if the patient did not reach the pre-defined improvement of 5% in MOS. Computed tomography of the brain and a plain X-ray were done, and if there were still doubts about a functioning shunt, a CSF-dynamic test was performed.

**MR Acquisitions**

In Studies I and II all MR measurements were performed using an Achieva 1.5 T MR scanner (Philips, Best, The Netherlands), and an eight-channel SENSE head coil. The same MR acquisition protocol was used before and after the shunt operation.

MRS data were acquired using Point Resolved Spectroscopy (PRESS), with an echo time of 30 ms and a repetition time of 3 s. 128 water-suppressed spectra were averaged, two MRS volumes of interest (VOI), one in the left thalamus and, one in the left FDWM, were placed in each subject, each voxel having a volume of ca. 2.50 mL (Figure 9. and 10.). In addition, spectra without non-water suppression were also obtained. For quantification of $R_2$ (1/T2), an axial multi-echo GRASE (ME-GRASE) pulse sequence was used to acquire data on the tissue water signal (= ME-GRASE-Volume), with resolution 2 x 2 x 4 mm$^3$, 8 equidistant spaced echoes 20-160 ms, and TR 5.28 s.

**MRS Quantification**

The MRS signals were analysed using LCModel version 6.1-4G in study I and version 6.2 in study I. The unsuppressed water signal were used as an internal reference, relaxation effects were calibrated using the $R_2$ map obtained from the ME GRASE sequence and absolute aqueous fraction concentrations was estimated. Absolute concentrations of the following metabolites were determined: tNA, NAA, tCr, tCho, mIns, Glu, and Lac. It should be noted that the calculated absolute concentrations were expressed as the concentration in the aqueous tissue fraction (mM aq.), not in the total MRS-VOI.

![Figure 9. Schematic placement of a single VOI in the FDWM of an iNPH patient in the cardinal directions of the localiser images.](image)
**Figure 10.** Schematic placement of a single VOI in the thalamus of an iNPH patient in the cardinal directions of the localiser images.

In *Study III* there were 33 consecutive patients, 17 males and 16 females, with a mean age of 73 years (range 49-81). Thirteen patients never underwent a second actigraphy recording. The reasons for this were: subdural haematoma (2) epidural/subdural haematoma postoperatively (2), and an intracerebral perioperative haematoma (1). Three (3) patients developed shunt dysfunction. There was also one (1) incomplete recording and one (1) patient was excluded due to severe back pain. Finally, three (3) patients never had surgery; one declined surgery, one had a negative preoperative examination and the third violated the protocol.

In this study, 17 HI, 8 males and 9 females with a mean age of 73 years (range 62-89) were controls. One individual experienced technical problems during the second recording session.

In *Study IV*, 35 patients, 16 males, 19 females, with mean age of 73 (49-81) were included. Twenty patients were evaluated preoperatively and three months postoperatively. Reasons for not being evaluated postoperatively were: five (5) haematomas (subdural, epidural/subdural and intracerebral) postoperatively; three (3) shunt dysfunctions (two proximal and one distal); three (3) patients refused either surgery (one) or a second posturography (two); three (3) were not evaluated a second time due to logistic reasons; and one (1) had a negative external lumbar drainage test and was not operated.

Sixteen HI, 7 males, 9 females aged 73 (62-89) were consecutively recruited as controls. expressed as the concentration in the aqueous tissue fraction (mM aq.), not in the total MRS-VOI.
**Actigraphy**

The SenseWear armband (BodyMedia Inc., Pittsburgh, PA, USA) was used for the actigraphic recordings. It was worn on the dominant upper arm for a week, the first time before the shunt operation and the second time three months postoperatively. The recordings were divided into daytime, from 8 a.m. to 7.59 p.m.; and nighttime from 8 p.m. to 7.59 a.m. The following variables were chosen to reflect activity and rest: steps/minute daily; Total energy expenditure (TEE)/minute daily; percentage lying down day and night; and percentage estimated sleep day and night. The HI also performed two one-week recording sessions with the SenseWear equipment at a three-month interval. The armband was only to be taken off during showers or baths in order to avoid contact with water. Both patients and HI were asked to fill in a short diary, recording time of waking and going to sleep, and the times of any daily naps. At least 3 days with a minimum of 90% successful recording for each 24-hour period was required for inclusion. For the HI the mean of the actigraphy parameters of the two recording periods was calculated.

**Computerised Dynamic Posturography**

Computerised dynamic posturography (CDP), Equitest (version 4.04. NeuroCom International, Clackamas, OR) was used, where the patient stands on a dual force plate and a visual surround is enclosed. The platform measures the force between the ground and the feet in a horizontal antero-posterior direction and from that the sway can be estimated. Patients and HI were examined under six separate conditions (Sensory Organising Test, SOT): 1. Eyes open, fixed surface and visual surround; 2. Eyes closed, fixed surface; 3. Eyes open, fixed surface, sway referenced visual surround; 4. Eyes open, sway referenced surface, fixed visual surround; 5. Eyes closed, sway referenced surface; and 6. Eyes open, sway referenced surface and visual surround (Figure 11.).

The SOT 1-3 were applied twice and the more difficult SOT 4-6 were applied three times. The average of the two SOT 1-3 runs and of the three SOT 4-6 runs was calculated. The subject had to maintain standing for at least 20 seconds. Each of the test items were scored according to the sway, where 100 is no sway and 0 means that the subject falls. When the subject failed to stand 20 seconds this was registered as Loss of Balance (LOB).
There is also a composite SOT score which is the weighted average of the scores of all sensory conditions, calculated as follows:

\[
(\text{mean(SOT 1)} + \text{mean(SOT 2)} + 3\times \text{mean(SOT 3)} + 3\times \text{mean(SOT 4)} + 3\times \text{mean(SOT 5)} + 3\times \text{mean(SOT 6)}) / 14
\] (Chaudhry, Bukiet et al. 2011)

The patients underwent the CDP before and three months postoperatively, and the HI twice with an interval of three months. For the HI the mean value of the two tests was calculated.

Figure 11. How the SOT 1-6 is performed. (Image courtesy of Natus Medical Inc.)
Statistics

For descriptive statistics mean and range were used in Study I and in Studies II-IV median and range.

In Study I the statistical analysis software used was JMP 8.0 (SAS Institute Inc., USA). A full mixed linear model (MLM) was created with the three fixed factors “Group”, “Tissue”, “Lateral”, and the corresponding crossing effects. A random factor “Patient” nested with the “Group” factor was also included. The Restricted Maximum Likelihood (REML) was used to analyse the mixed model. The model gave no significant effects for the “Lateral” effect or any of its crossing effects. Therefore, the model was subsequently reduced to contain only the “Group”, “Tissue”, their crossing effect, and the “Patient” effect.

From the MLM mean values of the crossing Effect, Group and Tissue were calculated (HI-FDWM, HI-thalamus, iNPH-FDWM, and iNPH-thalamus). Differences in mean values were tested using a Tukey test, and p-values < 0.05 were considered significant.

Linear regression models were created using the motor variables: w10mt, w10ms, TUGt and TUGs as explanation variables for the metabolite concentrations NAA, tNA, Glu, tCr, tCho, Lac, mIns and the mean R2 as response variables. For patients for whom two MRS measurements were made from the same tissue, the mean values were used as response variables. All models were created using the standard least square method in JMP. Variables were considered significantly correlated for p < 0.05.

In Study II statistical tests were performed using GraphPad Prism version 5.0a (GraphPad Software, San Diego California USA). The averaged concentration values of the right and left voxels was used.

The mean difference between HI and patients were tested using an equal variance, two tailed t-test, and the difference pre- and postoperative was tested using a paired t-test. P values <0.05 were considered significant.

The estimated metabolite concentrations and R2 were tested for correlation with the motor scores w10mt, w10ms, TUGt, TUGs and also the MOS values. Evan’s index was also tested for correlation with the metabolites and R2. Correlations with p<0.05 were considered significant.

In Study III statistical calculations were performed in R Version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org.). Non-parametric statistics
(i.e., Wilcoxon and Mann-Whitney where appropriate) were used to compare the patients to HI as well as to compare patients pre- and postoperatively. Pearson’s product-moment correlation was used.

In *Study IV* an a priori power-analysis calculated for this study indicated that at least 16 individuals in each group were needed in order to detect a significant difference for the SOT at 80% power and $\alpha=0.05$. Minitab 16 Statistical Software (Minitab Inc.) was used for statistical calculations. Non-parametric statistics, Mann Whitney U and Chi squared test for unpaired data and Wilcoxon sign rank test and McNemar for paired data were used. Spearman's $\rho$ correlation coefficient was used for calculating correlations.
RESULTS
In Studies I-IV there were altogether 43 individual patients, 23 males and 20 females, with the characteristics outlined in Table V.

Table V. Clinical preoperative data for the iNPH patients in Study I-IV

<table>
<thead>
<tr>
<th>All iNPH patients (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age (mean year, range)</td>
</tr>
<tr>
<td>Disease duration (mean months, range)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
</tr>
<tr>
<td>Hypertension (n)</td>
</tr>
<tr>
<td>Stroke (n)</td>
</tr>
<tr>
<td>Heart disease (n)</td>
</tr>
<tr>
<td><strong>Gait</strong></td>
</tr>
<tr>
<td>w10mt (mean seconds, range)</td>
</tr>
<tr>
<td>w10ms (mean steps, range)</td>
</tr>
<tr>
<td>TUGt (mean seconds, range)</td>
</tr>
<tr>
<td>TUGs (mean steps, range)</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
</tr>
<tr>
<td>MMSE (mean, range)</td>
</tr>
</tbody>
</table>
**Study I**

At baseline there was a mean 11% lower (p = 0.02) NAA and 6% lower tNA (p = 0.05) in the thalamus in the patient group compared to the HI group (Table VI.). There were no significant differences between the groups for the FDWM. Metabolite ratios to tCr were not significantly different in either the FDWM or the thalamus compared to HI. An increased tCr in FDWM correlated to a reduced motor function. A borderline significant negative correlation, i.e. lower NAA correlated to a reduction in motor function, was found in the thalamus. Elevated lactate levels were not detected in the thalamus or the FDWM. The patients performed worse in motor functions, while MMSE was similar (Table VII.).

No significant differences between R2 in different tissues and subjects were observed. This suggests that there was no significant difference in the intracellular aqueous state between the groups and different tissues.

**Table VI. Study I.** Mean and standard error of metabolite concentrations in the thalamus in patients and HI. Concentration values are presented in units of mM aq. n.s. = not significant.

<table>
<thead>
<tr>
<th></th>
<th>iNPH (n=15)</th>
<th></th>
<th>HI (n=16)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA</td>
<td>9.69</td>
<td>(SE) 0.26</td>
<td>11.01</td>
<td>(SE) 0.31</td>
</tr>
<tr>
<td>tNA</td>
<td>12.01</td>
<td>(SE) 0.23</td>
<td>13.04</td>
<td>(SE) 0.28</td>
</tr>
<tr>
<td>Glu</td>
<td>12.47</td>
<td>(SE) 0.42</td>
<td>13.33</td>
<td>(SE) 0.51</td>
</tr>
<tr>
<td>tCr</td>
<td>7.94</td>
<td>(SE) 0.20</td>
<td>8.27</td>
<td>(SE) 0.20</td>
</tr>
<tr>
<td>tCho</td>
<td>2.39</td>
<td>(SE) 0.10</td>
<td>2.57</td>
<td>(SE) 0.11</td>
</tr>
<tr>
<td>Lac</td>
<td>0.41</td>
<td>(SE) 0.13</td>
<td>0.36</td>
<td>(SE) 0.16</td>
</tr>
<tr>
<td>mIns</td>
<td>7.18</td>
<td>(SE) 0.33</td>
<td>6.57</td>
<td>(SE) 0.38</td>
</tr>
</tbody>
</table>
Table VII. Clinical results for iNPH patients and HI in Study I.

<table>
<thead>
<tr>
<th></th>
<th>iNPH (n=15)</th>
<th>HI (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gait</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>w10mt (mean sec, range)</td>
<td>16 (8-29)</td>
<td>7 (5-8)</td>
</tr>
<tr>
<td>w10ms (mean steps, range)</td>
<td>26 (16-42)</td>
<td>10 (9-13)</td>
</tr>
<tr>
<td>TUGt (mean sec, range)</td>
<td>21(8-36)</td>
<td></td>
</tr>
<tr>
<td>TUGs (mean steps, range)</td>
<td>28(12-43)</td>
<td></td>
</tr>
<tr>
<td>Gait scale 1-6</td>
<td>4 (1-6)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Balance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romberg 0-60 (mean seconds, range)</td>
<td>22 (0-60)</td>
<td>60 (60)</td>
</tr>
<tr>
<td><strong>Urgency</strong></td>
<td>11/16</td>
<td>nd</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE 0-30</td>
<td>27 (24-30)</td>
<td>29 (27-30)</td>
</tr>
</tbody>
</table>

**Study II**

tCho increased in the FDWM after shunt surgery (p=0.01) (Table VIII.). mIns tended to decrease (p=0.06). Lac was decreased postoperatively, though not significantly. R₂ did not change.

There were no changes in the thalamus for any of the metabolites after surgery. Compared to HI, the postoperative NAA remained decreased (p=0.04), while tNA was only slightly decreased (p=0.07). R₂ was not changed. Lactate was decreased, but not to a significant level.

Volumetric assessment showed a significant decrease in volume of the lateral ventricles, median 16%.

We found a borderline positive (p=0.06) correlation (r=0.51) between the change in motor score and the reduction in ventricular volume.
The change in Glu concentration postoperatively was significantly positively correlated to MOS in the thalamus (p<0.05), thus the higher the MOS, the greater the difference in Glu concentration.

Twelve out of 14 patients were responders (86%). All fourteen patients showed a median improvement in MOS of 23% (Table IX.). One of the non-responders showed a reduction in ventricular volume consistent with a patent shunt. In the other patient, a CSF-infusion study was performed showing shunt malfunction.

**Table VIII. Study II.** Mean and standard error of metabolite concentrations in the frontal deep white matter in iNPH patients at baseline and after shunt surgery, and healthy individuals (HI).

<table>
<thead>
<tr>
<th></th>
<th>iNPH baseline (n=14)</th>
<th>iNPH after shunt surgery (n=14)</th>
<th>HI (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
</tr>
<tr>
<td>NAA</td>
<td>9.41</td>
<td>0.30</td>
<td>9.39</td>
</tr>
<tr>
<td>tNA</td>
<td>10.54</td>
<td>0.30</td>
<td>10.51</td>
</tr>
<tr>
<td>Glu</td>
<td>10.04</td>
<td>0.45</td>
<td>9.70</td>
</tr>
<tr>
<td>tCr</td>
<td>7.76</td>
<td>0.25</td>
<td>7.62</td>
</tr>
<tr>
<td>tCho</td>
<td>2.67*</td>
<td>0.11</td>
<td>2.79*</td>
</tr>
<tr>
<td>Lac</td>
<td>0.61</td>
<td>0.16</td>
<td>0.49</td>
</tr>
<tr>
<td>mIns</td>
<td>8.15</td>
<td>0.30</td>
<td>7.70</td>
</tr>
</tbody>
</table>

Concentration values are presented in units of mM aq. NAA (N-acetylaspartate), tNA (total N-acetyl aspartate), Glu (Glutamate), tCr (total Creatine), tCho (total Choline), and Lac (Lactate), mIns (myo-Inositol). * p < 0.05 paired t test significance of difference between baseline and after shunt surgery.
Table IX. Study II. Median and (range) of motor function, Evan’s index, and lateral ventricle volume at baseline and after shunt surgery. Improvement is given as the percentage decrease between baseline and after shunt surgery.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Postoperative</th>
<th>Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>w10mt (sec)</strong></td>
<td>15.0 (7.5–29.0)</td>
<td>9.0 (6.0–20.0)</td>
<td>20.7 ** (-10–94.4)</td>
</tr>
<tr>
<td><strong>w10ms</strong></td>
<td>25.0 (16.0–42.0)</td>
<td>17.5 (14.0–31.0)</td>
<td>21.1 ** (-6.3–59.0)</td>
</tr>
<tr>
<td><strong>TUGt (sec)</strong></td>
<td>19.5 (8.5–36.0)</td>
<td>12.0 (7.0–34.0)</td>
<td>25.6 ** (-11.0–71.0)</td>
</tr>
<tr>
<td><strong>TUGs</strong></td>
<td>29.5 (12.0–43.0)</td>
<td>17.0 (12.0–37.0)</td>
<td>26.9 ** (-25.0–69.2)</td>
</tr>
<tr>
<td><strong>MOS</strong></td>
<td></td>
<td></td>
<td>22.6 †† (-9.7–67.5)</td>
</tr>
<tr>
<td><strong>Evan’s index</strong></td>
<td>0.38 (0.31-0.49)</td>
<td>0.37 (0.31-0.48)</td>
<td>3.0 (-4.8–15.1)</td>
</tr>
<tr>
<td><strong>Volume (L)</strong></td>
<td>0.13 (0.08-0.22)</td>
<td>0.11 (0.06-0.18)</td>
<td>15.9 ** (13.1–39.7)</td>
</tr>
</tbody>
</table>

** p < 0.01, Wilcoxon matched pairs test, †† p < 0.01 Wilcoxon signed rank test median difference from 0.

Study III

The 33 patients took fewer steps during the daytime (p<0.001) and TEE was lower in the daytime (p<0.01) prior to shunt operation, compared to the HI. There were no significant differences between the patients and the HI regarding time lying down and estimated sleeping time (Table X.). The 33 patients had poorer gait function (w10t, w10s, TUGt, TUGs) (p<0.001) and lower MMSE (p<0.001) compared to the HI. There was no correlation between preoperative steps in the daytime and MOS or MMSE with MOS.

Twenty patients completed the three-month postoperative SenseWear recording. In these 20 patients there were no significant changes concerning the number of steps, TEE, time lying down and duration of sleep after surgery (Table XI.). Eighty-five per cent were responders who had a mean improvement of 26% (5-49) in MOS. MMSE was not significantly changed. The correlations between the first and second recordings in HI for all variables were strong: correlation coefficient steps daily r=0.88, TEE daily r=0.78, lying down during the day r=0.92, sleep during the day r=0.91, lying down at night r=0.91, sleep at night r=0.88.
Table X. Study III. Actigraphy: iNPH-preoperatively vs. HI. Values are given as median (range)

<table>
<thead>
<tr>
<th></th>
<th>iNPH preop (n=33)</th>
<th>HI (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime (8 a.m.-7.59 p.m.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steps/min</td>
<td>2.6 (0.1-11.9)</td>
<td>8.9 (4.3–17.4) ***</td>
</tr>
<tr>
<td>TEE kcal/min</td>
<td>1.3 (1.0–3.0)</td>
<td>1.8 (1.0–2.4) **</td>
</tr>
<tr>
<td>Lying down, %</td>
<td>4.9 (0.3-35.8)</td>
<td>2.9 (0-17.2)</td>
</tr>
<tr>
<td>Sleep, %</td>
<td>3.1 (0-32.6)</td>
<td>2.0 (0-7.1)</td>
</tr>
<tr>
<td><strong>At night (8p.m.-7.59 a.m.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down, %</td>
<td>66.4 (36.6–88.5)</td>
<td>67.1 (24.6–86.6)</td>
</tr>
<tr>
<td>Sleep, %</td>
<td>52.6 (26.0–80.7)</td>
<td>55.8 (19.2–72.0)</td>
</tr>
</tbody>
</table>

**=p<0.01, ***= p<0.001
Table XI. Study III. Actigraphic parameters pre- and post-operatively in iNPH patients. Values are given as median (range)

<table>
<thead>
<tr>
<th></th>
<th>iNPH preop n=20</th>
<th>iNPH postop n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime (8 a.m.-7.59 p.m.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steps/min</td>
<td>2.7 (0.1-11.9)</td>
<td>2.1 (0.2 – 7.7)</td>
</tr>
<tr>
<td>TEE kcal/min</td>
<td>1.4 (1.0–2.2)</td>
<td>1.4 (1.0 – 2.1)</td>
</tr>
<tr>
<td>Lying down, %</td>
<td>4.6 (0.3 - 35.8)</td>
<td>7.0 (0.4 – 16.4)</td>
</tr>
<tr>
<td>Sleep, %</td>
<td>2.7 (0.0 – 32.6)</td>
<td>3.5 (0.1 – 9.9)</td>
</tr>
<tr>
<td><strong>At night (8p.m.-7.59 a.m.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down, %</td>
<td>66.3 (36.7 – 88.5)</td>
<td>71.5 (43.3 – 86.1)</td>
</tr>
<tr>
<td>Sleep, %</td>
<td>52.6 (26.3 - 80.7)</td>
<td>57.0 (24.7 – 73.5)</td>
</tr>
</tbody>
</table>

**Study IV**

Preoperatively the 35 patients had a lower SOT score in all six conditions (p=0.01 for SOT 1 for SOT 2-6 p<0.001) compared to the HI. The greatest differences were seen in conditions 5 and 6 (Figure 12.). LOB was very frequent in SOT conditions 5 and 6 in iNPH preoperatively and the difference compared to HI was highly significant (Figure 13.). Preoperatively the patients showed significantly inferior gait capacity, had lower Romberg test scores, and performed a lower MMSE than the HI.

Twenty patients were evaluated preoperatively and three months postoperatively. There was a significantly improved composite score (p<0.05) but no change in any of the SOT conditions after shunt surgery (Figure 14.). LOB was not reduced significantly after shunt operation (Figure 15.).

Ninety per cent (5-67) of the patients were considered responders, with a mean improvement in motor score of 26%.
**Figure 12. Study IV.** Sensory Organising Test (SOT). Comparison is made between the mean SOT score for HI-1 and HI-2 (the first and second examination) and the preoperative SOT score for iNPH. Values are given as median. Interquartile range is indicated. **=p<0.01, ***p<0.001.

**Figure 13. Study IV.** Loss of Balance (LOB) for each SOT condition for iNPH preoperatively versus HI-1 and HI-2 (the first and second examinations) respectively. ***=p<0.001
Figure 14. Study IV. Sensory Organising Test for iNPH pre- vs. postoperative. Median and interquartile ranges are given. *= p<0.05.

Figure 15. Study IV. Loss of Balance (LOB) for each SOT condition for iNPH preoperatively vs. iNPH postoperatively. No significant change of LOB pre- and post-operative.
DISCUSSION

The pathogenesis of iNPH is still largely unexplained despite nearly 50 years passing since the description of Hakim and Adams. For reasons previously discussed in this thesis, our current knowledge points to the frontal deep white matter, thalamus and the basal ganglia as being locations where neuronal function appears to be impaired, probably because of disturbed metabolism, resulting in the development of iNPH symptoms. We therefore designed two studies, before and after a shunt operation, using MRS to study metabolism in the FDWM and the thalamus.

We also wanted to investigate some aspects of the clinical symptomology from a new perspective; the long term gait capacity and sleeping/resting behaviour in patients before and after shunt surgery. Furthermore, a more detailed and quantified study of one of the main symptoms, namely the postural dysfunction, before and after shunt surgery.

Selection of Patients and Diagnostic Criteria

The patients who participated in this study were consecutively included from the South-eastern Region of Sweden, a catchment area with 1 million inhabitants (http://www.scb.se). The mean age and the gender distribution were in accordance with previous studies on iNPH.

Patients fulfilling the diagnostic criteria for iNPH as formulated in the Eu-iNPH study, or criteria for probable iNPH according to the Am-iNPH guidelines with small modifications, were included. The MMSE should be between 21-30 in the MRS-studies (a criterion in the Eu-iNPH study for “typical iNPH” was that MMSE was ≥ 21), we did not have a CSF pressure lower limit of 5 mmHg, and finally an Evan’s index of ≥0.30 was allowed instead of > 0.30. The reason for excluding patients with low cognitive function was to have as pure form of iNPH as possible for the MRS studies, since it has been shown that cognitive impairment is related to other pathologies such as Alzheimer’s disease and/or vascular dementia (Golomb, Wisoff et al. 2000; Hellstrom, Edsbagge et al. 2008; Cabral, Beach et al. 2011). In the Am-iNPH guidelines a lower limit of CSF pressure is set up but no scientific basis for choosing that limit are presented, and according to the Eu-iNPH study no such limits were applied. In the original Eu-iNPH report a limit for Evan’s index was set at ≥ 0.30, which we have followed in this study. The same limit is also discussed in the Am-iNPH guidelines, but there is a greater stress on ventricular enlargement and they state” > 0.30 or comparable measure”. Even if the patient fulfills the strict criteria of iNPH, concurrent disease may also imitate the symptoms of iNPH, which makes a definite diagnosis of iNPH difficult. Another
problem in diagnosing iNPH is to distinguish between iNPH and sNPH, unless there is a clear history of an antecedent subarachnoidal bleed or bacterial meningitis.

In order to mimic the normal clinical situation we decided to let the patients go through the usual procedures (Figure 16.) that we perform when we examine patients at the Hydrocephalus Unit. Following this a decision at a treatment conference, where both a neurologist and a neurosurgeon are present, is made if the patient should be offered a shunt operation. This decision is based on clinical, radiological and physiological examination i.e. a tap test or a combination of tap test and lumbar infusion, or occasionally an ELD test.

This means that patients may fulfill the criteria for probable iNPH, but in the consensus discussion at the treatment conference there may be aspects such as an increased operative risk that will lead to the conclusion that the risk for the patient is too high. A negative ELD test that strongly indicates a poor postoperative outcome will also result in not offering a patient a shunt operation.

This concept obviously may involve bias, but we chose this strategy in order to include patients according to normal clinical practice.

**Size of the Study Populations**

Prior to the study we only performed a power analysis for *study IV*. The calculation indicated that we at least needed 16 subjects in each group to be able to show a significance at $\alpha=0.05$ with 80% power. For the other studies we did not perform an a priori power analysis. For *study I* and *II* the method was new and it was therefore difficult to estimate standard deviations. We believed that the method could possibly show a difference of about 10% and from that we decided to include at least 10 subjects in each group. A post hoc power analysis revealed that the subjects needed to show significance at $\alpha=0.05$ with 80% power were quite different between the metabolites, but for NAA 12 and for tNA 16 subjects in each group should be needed to show this difference. Concerning *study III* we unfortunately did not perform any analysis of the number of subjects needed to show a significant difference but thought that about 20 subjects would be sufficient.
Representativity of the Healthy Individuals

Ideally the recruitment of HI should have been matched for age and sex, but we thought it would not be feasible due to a too complicated and time consuming procedure. We therefore consecutively recruited HI from friends and relatives to staff members at the clinic. That they had approximately the same age and gender distribution as the iNPH patients was incidental. They were subjectively healthy, which did not preclude previous disease as long as it did not impair gait and cognition. Their gait performance for comfortable walking was slightly higher than has been reported. In our studies around 140 cm/sec compared to about 130 cm/sec for the age group 70-79 years old (Bohannon 1997). Normative values for MMSE in a British
population-based study was 28.3 for highly -, and 27.5 for poorly educated 70-74 years old men (Huppert, Cabelli et al. 2005) compared to 29 for our HI. These figures indicate our HI to be representative both for cognitive and gait function in their age group. One drawback of our study is that the HI were only examined once, calculating the average of two tries, for w10mt and w10ms, but the reliability of walking this distance at a comfortable pace has been shown to be very high, which is why this could be regarded a minor issue (Green, Forster et al. 2002). The loss of HI was small; one HI´s data was lost due to computer error in Studies I and II and the second recording of one HI was lost due to a technical problem. One HI only participated in Studies I and II, and one HI only participated in Studies I-III, both due to unwillingness to take part in these studies. Not all HI were intended to participate in Studies I-II.

**Validity of Clinical Tests**

Clinical evaluation, including a fixed protocol for neurological signs, was first made by a neurologist (FL) and this formed the basis for inclusion in the study. Examination of gait and cognition was later made by physiotherapists and occupational therapists connected with the Hydrocephalus Unit, who are especially trained to examine hydrocephalus patients. The tests chosen for evaluation have been validated and previously used with this group of patients such as in the Eu-iNPH study (Mathias, Nayak et al. 1986; Green, Forster et al. 2002; Klinge, Marmarou et al. 2005). In the MRS studies an independent neuroradiologist assessed the MRI, but in Studies III and IV we relied on the original interpretation of the radiologist.

**Outcome of Shunt Surgery**

As pointed out previously there are obvious shortcomings in the area of evaluation of outcome in iNPH. A promising tool for future evaluation both clinically and scientifically is the recently published iNPH scale (Hellstrom, Klinge et al. 2012). This is based on experience from the Eu-iNPH study where at least a 5 % improvement in a weighted total iNPH score including subscales for gait (weighted twice as much as the other symptoms), balance, neuropsychology and micturition is advocated. We have adopted a modified version of this concept and we have defined a positive response as a 5% improvement in a motor score, MOS, calculated as a composite score with the percentage change of each item expressed as follows:

\[ \Delta w10mt + \Delta w10ms + \Delta TUGt + \Delta TUGs) / 4 \]
The reason for constructing this MOS was to include more than one aspect of motor function and also to make the outcome less dependent on temporary variations in individual items. The choice of items included was based on reports from previous studies (Blomsterwall, Svantesson et al. 2000; Hellstrom, Edsbagge et al. 2008; Tisell, Tullberg et al. 2011). The reason for not including other domains in the outcome measure was partly because at the time we started this project we did not have neuropsychological expertise and could, therefore, not use more elaborate neuropsychological instruments other than MMSE, and partly because gait is the main symptom that is also most likely to improve after a shunt operation. With our definition of positive postoperative outcome the improvement rate was: 86% in Study II; 85% in Study III; and 90% in Study IV. First of all it must be stressed that due to different inclusion criteria and different outcome measures of shunt surgery a comparison with other studies should be cautiously performed. However our results seem to be much better than those reported by Hebb et al. in the systematic review of diagnosis and outcome from 2001, having an overall improvement of 59% (24-100) (Hebb and Cusimano 2001). Our results were also better than those reported recently in the Eu-iNPH study (Klinge, Hellstrom et al. 2012). The cut-off level is naturally vital for how good the results are, and 5% improvement may be regarded as low, but even if we had used a higher cut off e.g. 10% our figures would have been 80% improvement rate, which is much better than those reported by Hebb and Cusimano.

To summarise: the consecutive inclusion of patients from a large catchment area, the fulfillment of the iNPH-criteria according to the Am-iNPH guidelines, though slightly modified, the age and gender distribution, the achievements on clinical tests, the improvement rates makes us believe that our patients are representative of iNPH patients in general.

**Test of Shunt Function**

The outcome of surgery may be negatively affected by malfunction of the shunt, but according to our procedure we considered the shunt as functioning if the patient reached the pre-defined improvement in MOS. If it was not reached, computed tomography and plain radiography of the shunt were performed and if there was no significant decrease in Evan’s index a CSF infusion test was performed. We thus strongly believe that all shunts were working as expected.
Complication Rate and Drop-Outs
Clinical studies attempting to follow the normal course of events after shunt operation have inherent problems with the risk of loss of research subjects, especially elderly fragile patients with concurrent disease and a higher risk for complications. Complication rates are known to be high in shunt surgery, according to Hebb et al. 38% (Hebb and Cusimano 2001), but recently larger studies show considerably lower figures. Twenty-eight per cent of patients experienced complications in the Eu-iNPH study, and were either conservatively (13%) or surgically (15%) treated (Klinge, Hellstrom et al. 2012). In the study by Poca et al. the mortality rate was 0.8%, early complications were found in 5.3% and six months after shunting there were asymptomatic hygromas in 3.4%. Further postsurgical complications were found in 3% (Poca, Solana et al. 2012). The complication rates in our studies were 21% in Study II, 26% in Study III and 25% in Study IV i.e. figures comparable with the Eu-iNPH study. The high postoperative complication rate stresses the importance of being strict when diagnosing iNPH, and also being careful when dealing with very old patients with serious medical problems that increase perioperative risk when the fact is that this group is also less likely to gain substantially from a shunt operation (Kahlon, Sjunnesson et al. 2007; Lemcke and Meier 2012). Unfortunately the drop-out rate was high in Studies III and IV for various reasons outlined in the methods section. The drop-outs were the same age as those who completed the studies and the sex distribution was almost equal, but they had slightly better gait function, which would not have had a major influence on the results. Because few patients were included it is difficult to draw any firm conclusion about differences in cardiovascular comorbidity, but the distribution was approximately equal between the drop-outs and those who completed the study protocol.

Magnetic Resonance Spectroscopy
CBF studies in iNPH have shown both a generally decreased CBF (Owler and Pickard 2001) but also regional pattern with decreased CBF in the frontal lobes, thalamus and the basal ganglia (Owler, Momjian et al. 2004). The function of the thalamus is complex; processing information passing from the basal ganglia to the cortex and giving rise to corticothalamic projections from the thalamus back to the basal ganglia (Haber and McFarland 2001).

As discussed in the introduction, absolute quantification is the most reliable way to analyse metabolites in the brain (Schirmer and Auer 2000; Li, Wang et al. 2003) than using Cr ratios since the concentration of Cr are not stable due to inborn errors of metabolism and kidney disease which may affect Cr concentration (Soares and Law 2009). The same pattern can also
be seen in Table VII where the standard error for Cr is at least as large as for the other metabolites. *Studies I and II* are the first to use this technique in iNPH, and furthermore they are also the first to analyse the thalamus in iNPH in a systematic way.

In the MRS studies (*I, II*) the main findings indicate, through decreased concentrations of tNA and NAA, that the thalamus may be involved in the pathological process even though there were no signs of normalisation after shunt diversion of CSF. Surprisingly we did not find decreased levels of tNA and NAA in the FDWM, but the explanation for this might be methodological since our results were based on absolute quantification whereas all previous research has been performed using ratios. Another possibility is that previous studies have included patients with lower cognitive function introducing the possibility of other neuropathology such as Alzheimer’s disease. Compared to the study from Lenfeldt et al. our voxels were much smaller than theirs, and compared with the study by del Mar Matarin et al. placement of voxels was not exactly the same. Postoperatively we could find no sign of normalisation of tNA and NAA. NAA is regarded as a neuronal density marker and evidence exists that low NAA can be reversed (De Stefano, Matthews et al. 1995; Bartsch, Homola et al. 2007). MRS studies in iNPH have provided diverging results where del Mar Matarin et al. found an increased postoperative NAA/Cr whereas Shiino et al. could not. There are several possible explanations for this. The low tNA and NAA before surgery might have been due to dysfunction in the basal ganglia for example, three months might be a too short time to be able to observe a significant change, the use of ratios might have obscured the results, and finally tNA and NAA might not reflect only motor function in the thalamus. Concerning the issue of Cr ratio we included a calculation in *Study I*, resulting in no differences for either the thalamus or the FDWM. Postoperatively, however, we found an increase in Cho in FDWM. Cho is involved in membrane function processes (Ross and Sachdev 2004) and CDP-choline, a precursor of Cho, is a neuronal repair agent (Barrachina, Dominguez et al. 2003). We are thus inclined to interpret the change as a sign of metabolic restoration. There was also a tendency towards a decrease in mIns. Myo-inositol is believed to be a glia cell marker (Ross and Sachdev 2004) and elevated concentrations have been reported in multiple sclerosis (Chard, Griffin et al. 2002) and Alzheimer’s disease (Kantarci 2007), and have been interpreted as enhanced gliosis. A decrease as we found could thus be interpreted as a sign of metabolic recovery.

To summarise: significantly decreased tNA and NAA levels indicate that the thalamus may be involved in the pathogenesis of iNPH. Even if a move towards normalisation of these
metabolites would have strengthened this hypothesis, it may still be valid. We have also found a significant increase in Cho and a borderline significant decrease in mIns in FDWM, which could be interpreted as a sign of recovery. Both these findings support the hypothesis that the cortico-basal ganglia-thalamocortical circuit is disturbed in iNPH. Future studies should focus on other locations in this circuit such as the basal ganglia, in particular the nucleus caudatus where higher magnetic field strength could provide additional information.

**Actigraphy**

So as to study the activity of patients and HI in their home environment, and to see the impact of a shunt, we used the actigraphy technique. The advantage is that monitoring continues day and night rather than just a few seconds with e.g. the 10 metre walk test. Actigraphy is a method that can estimate energy expenditure, gait, and time spent lying and sleeping. It is a convenient alternative method to indirect calorimetry, which is the gold standard (Haugen, Chan et al. 2007). Another alternative, self-reporting questionnaires on physical activity, are better suited for studying larger populations and its role is not established for small populations according to a recent review (Neilson, Robson et al. 2008). SenseWear has been validated for young males (Fruin and Rankin 2004) where comparison with indirect calorimetry was performed showing that the methods were highly correlated when resting, and no significant differences when exercising though the correlation was weak with overestimation while walking on flat ground and underestimation when walking on an incline. In another larger validation study including both males and females there was underestimation of daily energy expenditure but the intra-class coefficient was high r=0.81 (St-Onge, Mignault et al. 2007). SenseWear has also been validated for resting energy expenditure in a group of 49 elderly adults (60-87 years) where 12-14 % overestimation was found compared to indirect calorimetry (Heiermann, Khalaj Hedayati et al. 2011). In another study involving 19 subjects with a mean age of 82 years the individual total energy expenditure values correlated highly between SensWear and indirect calorimetry (r=0.893) (Mackey, Manini et al. 2011)

According to the American Academy of Sleep actigraphy was found valid and reliable in a Level I, Grade A study, and is thus recommended for detecting sleep in healthy adults. It is also considered useful in characterising and monitoring circadian rhythm patterns in elderly persons with or without dementia (Littner, Kushida et al. 2003). The method is not validated for iNPH-patients, but it has been validated for patients with certain diseases, e.g. chronic obstructive lung disease and with a low gait capacity (Hill, Dolmage et al. 2010), and this should apply for iNPH. In the actigraphy study we found that the patients had significantly
reduced ambulatory activity and lower energy consumption compared to HI. Surprisingly there were no differences in activity though they showed improvement in gait capacity when tested at a certain point in time. A greater need to sleep and a sopor- somnolence-coma disorder (SSCD) is according to the classification of Lindquist et al. an attribute of iNPH patients (Lindqvist, Andersson et al. 1993). In our study we could not find any differences concerning resting and sleeping times before and after surgery, or when compared with the HI. From the literature it is said that the number of steps taken per day is normally between 2000 and 9000, which means 1.4-6.25 steps/minute (Tudor-Locke, Hart et al. 2009). This places our patients in the lower normal range whereas our HI were more physically active than expected. A normal TEE for an elderly healthy person is estimated to be 2400 kcal/d (Poehlman 1992). The corresponding figure for our HI was 2520 kcal/d, which is close to the estimated value, and for our patients the figure was 1872 kcal/d.

Normative data on sleep in the elderly extracted from a large cross-sectional study shows that the median sleep time is approximately 7 hours/night (Ohayon and Vecchierini 2005). From our data, the median night-time sleep was 6 hours, though this must be interpreted with caution since our data came from actigraphy.

The correlation coefficients between the first and the second examination were strong, steps daily r=0.88, TEE daily r=0.78, lying down during the day r= 0.92, sleep during the day =0.91, lying down at night r=0.91, sleep at night r=0.88. This favours the reliability of the method.

We suspect that the reason the patients did not become more active after the shunt operation may be either lack of rehabilitation and/or that patients had developed habits that were difficult to change. A future study with actigraphy would be to see if a rehabilitation programme involving quality-of-life assessment can improve the patients’ ambulatory activity.

**Computerised Dynamic Posturography**

Gait and balance difficulty is a major symptom in iNPH. Even if it is a well-known symptom, there are few studies specifically addressing the issue of postural dysfunction. The existing evidence suggests that there is a great correlation between motor and balance function (Blomsterwall, Svantesson et al. 2000). iNPH patients have greater sway on a platform and there is a higher backward directed velocity of centre of pressure compared to HI. It has been claimed that balance is the symptom that improves the most after shunt surgery.
(Blomsterwall, Svantesson et al. 2000). The Equitest method has been used in several conditions and diseases (Chong, Horak et al. 1999; Ondo, Almaguer et al. 2006; Suttanon, Hill et al. 2012) and is regarded as the best way of examining balance. The test-retest variability has been studied in 40 non-institutionalised older adults (mean age 74.8 years) and the intra-class coefficient (average of 3 trials) was for SOT 1: 0.51; SOT 2: 0.42; SOT 3: 0.26; SOT 4: 0.47; SOT 5: 0.68 and for SOT 6: 0.64 and for composite score 0.66. The authors used the criteria of Fleiss so the reliability should therefore be fair to good (0.4-0.75), for loss of balance (LOB) the per cent agreement was between 100 % in the easiest conditions and 85% in condition 5 and 77% in condition 6 (Ford-Smith, Wyman et al. 1995). Sensitivity for detecting a central nervous system dysfunction has been reported from retrospective studies, most of them with a limited number of patients, reporting a wide range from as low as 21% to 100 %, but the largest study involving 270 patients with a central nervous system dysfunction showed a sensitivity of 50% (Di Fabio 1995). In a large prospective study examining 260 older non-institutionalised persons to determine the predictive value of posturography for future falls, and including a comparison with standard clinical balance tests, there was a higher sensitivity for identifying recurrent fallers favouring posturography (Buatois, Gueguen et al. 2006).

The methodology used in our study is supported by the fact that the HI performed in accordance with a group aged <80 years in a previous study using the same (Camicioli, Panzer et al. 1997) and also that there was a rather high correlation between the first and the second test. The correlations for each SOT of the two examinations in the HI were: SOT 1: ρ=0.41; SOT 2: ρ=0.64; SOT 3: ρ=0.49; SOT 4: ρ=0.58; SOT 5: ρ=0.65; SOT 6: ρ=0.53. The main findings were that the patients exhibited a profound impairment of balance with a large difference of Loss of Balance (LOB) on SOT 5 and 6 between the patients and the HI which indicates a central vestibular dysfunction, and that the patients only experienced a minor improvement in postural function after shunt surgery. When looking at Figures 9 and 11 the visual impression is that there is a tendency towards better balance, though the number of patients was probably too small to provide significance. It is possible that the patients do improve their postural function but perhaps not so much as previously believed. Further studies on balance should include a larger cohort of patients in order to be able to answer the question whether balance is improved by a shunt operation and if so, to what extent. Another important question is if CDP may be used to predict falls in iNPH patients and thus strengthen the indication for a shunt operation.
CONCLUSIONS

Magnetic Resonance Spectroscopy

- $^1$HMRS with absolute quantification was used for the first time in iNPH.
- A decreased thalamic tNA and NAA indicates neuronal dysfunction, which supports the hypothesis that there is a disturbed cortico-basal ganglia-thalamocortical circuit.
- In contrast to previous findings there were no metabolic differences in FDWM between patients and HI at baseline.
- There was no increase in tNA and NAA in the thalamus after shunt surgery.
- A postoperative significant decrease in Cho and a borderline significant decrease in myo-Ins in FDWM could be interpreted as signs of metabolic recovery.

Actigraphy

- Actigraphy showed that iNPH patients have a significant lower ambulatory activity and decreased TEE compared to HI.
- In contrast to previous assumptions we could not find that time spent resting and sleeping differed significantly between the patients and HI.
- There was no change of ambulatory activity, TEE or resting/sleeping behaviour after shunt surgery, which may be attributed to strong habits and/or lack of rehabilitation.

Computerised Dynamic Posturography

- iNPH patients had a profound postural disturbance compared to HI as measured with Equitest Computerised Dynamic Posturography.
- The most difficult test items, SOT 5 and SOT 6, reflecting vestibular function were at the most impaired indicating central vestibular dysfunction.
- Patients frequently showing Loss of Balance on the difficult tests SOT 5 and SOT 6, may be seen as a predictor for future falls.
- Surgery resulted in only slight improvement in balance was seen after shunt surgery in contrast to previous reports.
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