LIST OF PUBLICATIONS

This thesis is based on the following articles, which are referred to by their Roman numerals.

I. Hellström P, Edsbagge M, Archer T, Tisell M, Tullberg M, Wikkelsø C.
The neuropsychology of patients with clinically diagnosed idiopathic normal pressure hydrocephalus.
Neurosurgery 2007 Dec;61(6):1219-26; discussion 1227-8.

II. Hellström P, Edsbagge M, Blomsterwall E, Archer T, Tisell M, Tullberg M, Wikkelsø C.
Neuropsychological effects of shunt treatment in idiopathic normal pressure hydrocephalus.
Neurosurgery 2008 Sep;63(3):527-35; discussion 35-6.

III. Hellström P, Klinge P, Tans J, Wikkelsø C.
Neuropsychological findings in the European study on iNPH.
Submitted to Clinical Neurology and Neurosurgery

IV. Klinge P, Hellström P, Tans J, Wikkelsø C.
Outcome in 142 iNPH patients included in the European Multicentre Study evaluated by the modified Rankin scale and a new iNPH scale.
Submitted to Acta Neurologica Scandinavica

CONTENTS

ABBREVIATIONS

AD ï Alzheimerôs disease
ADAS ï Alzheimer Disease Assessment Scale
AE ï American-European
AED ï Astheno-Emotional Disorder
BD ï Binswangerôs disease
CANTAB ï Cambridge neuropsychological test automated battery
CBF ï cerebral blood flow
CD ï Confusional Disorder
CI ï Confidence interval
C_{out} ï outflow conductance
CPs ï choroid plexuses
CPP ï cerebral perfusion pressure
cSAS ï cranial subarachnoid space
CSF ï cerebrospinal fluid
CT ï computerised tomography
DS ï Digit span
DWMH ï deep white matter hyperintensity
ETV ï endoscopic third ventriculostomy
ECF ï extracellular fluid
EI ï Evansô index
EMD ï Emotional-Motivational Blunting Disorder
FT ï Finger tapping
GD ï Gait disorder
HCDD ï Hallucination-Coenestopathy-Depersonalisation Disorder
HI ï healthy individuals
HVLT-R ï Hopkins Verbal Learning Test revised
ICP ï intracranial pressure
iNPH ï idiopathic normal pressure hydrocephalus
KAD ï Korsakov Amnestic Disorder
KI ï Kiefer index
KOLT ï Kendrick object learning test
KSS ï Kiefer Scale score
MMSE ï mini-mental state examination
MRI ï magnetic resonance imaging
NFL ï Neurofilament light protein
NPH ï normal pressure hydrocephalus
OPD ï organic psychiatric disorder
PAG ï periaqueductal grey
PET ï positron emission tomography
PVH ï periventricular hyperintensity
PMC ï pontine micturation centre
RAVLT ï Rey auditory verbal learning test
RC ï Radionuclide cisternography
ROCF ï Rey-Osterrieth Complex Figure
R_{out} ï resistance to outflow
RVV ï relative ventricular volume
SAE ï subcortical arteriosclerotic encephalopathy
SAS ï subarachnoid space
sd ï standard deviation
sNPH ï secondary normal pressure hydrocephalus
sSAS ï spinal subarachnoid space
SSS ï superior sagittal sinus
SSCD ï Somnolence Sopor Coma Disorder
VP ï ventriculoperitoneal
VV ï ventricular volume
WAIS-R ï Wechsler Adult Intelligence Scale revised
WMS ï Wechsler Memory Scale
WMS-R ï Wechsler Memory Scale revised
WT ï Ten word test

1. INTRODUCTION

1.1. Early cases and history

In 1957, after returning to the Hospital San Juan de Dios in Bogotá from a research fellowship in Boston, Salomón Hakim encountered a 16 year old boy who had been struck by a car. A subdural haematoma had been successfully evacuated through a posterior frontal burr hole. The cortex in the region of the operation appeared to be contused and there was a subarachnoid haemorrhage. The patient improved after the evacuation and a few days later his condition seemed stable. He was sent to his home for further convalescence. By that time he was able to move his arms and legs and at times he would open his eyes and look at people around him. But he did not vocalize or speak. A month later, having failed to improve further, he was readmitted at his fatherôs insistence. During the neurological examination he was now semicomatose. The investigations that followed showed that he had an enlarged ventricular system (indicated first by angiography and later by pneumoencephalography). The intracranial pressure, however, was normal (15 centimeters of water). Fifteen ml of cerebrospinal fluid (CSF) was removed for laboratory analysis, and on the following day the patient spoke for the first time since the subdural bleeding. A relapse into mutism and drowsiness after a few days motivated a second removal of CSF, which turned out to be as beneficial as the first one. A ventriculoartrial shunt was implanted and three and a half months later the boy had returned to school and was performing nearly as well as before the accident.

Another case had quite a different course of illness. During a period of one year a 52 year old professional trombonist experienced a progressive reduction of alertness, memory, and even speech. When he was first examined he had lost the ability to play his instrument, he was mentally dull and apathetic, showing no concern about his physical appearance or things that were happening. In parallel with the mental changes he had also developed a gait disorder with imbalance and stiff legs. He was incontinent of urine. When CSF was removed, again for the purpose of analysis of its contents, the patient had a normal CSF pressure of 18 centimeters of water. According to his wife the patient improved after the removal of CSF, both mentally and with regard to gait, but the condition worsened again after a few days. Another month passed during which he gradually got worse. Angiography was performed in order to rule out a chronic subdural haematoma. Findings of displacement and bowing of the anterior arteries gave rise to a suspicion of ventricular enlargement, which was later confirmed by a ventriculogram and pneumoencephalography. Following these investigations some 90-100 ml of CSF were drained and on the following day the patient was quiet and alert. On the 30th of March he received an occipital ventriculoartrial shunt and by the summer his mental status was considered quite normal. His gait was also markedly improved, but he still used a cane to feel safe (1).

The two vignettes represent hallmark cases of normal pressure hydrocephalus (NPH). The adolescent developed NPH secondary to a subarachnoid haemorrhage, whereas the trombonist suffered from idiopathic NPH (iNPH), i.e. the condition that is the focus of this thesis.

NPH, whether secondary or idiopathic, is a neurological disorder caused by a disturbance of CSF dynamics, and characterised by an enlarged ventricular system,

normal intracranial pressure and symptoms related to gait, balance, neuropsychology and continence. The first description of the syndrome appeared in Hakimôs thesis (2) and it was introduced to a broader public through two seminal articles in the summer of 1965 (3, 4). In the latter of these, Hakim and Adams presented three cases (the two patients briefly described earlier, and the case of a man who had suffered a skull fracture during a hunting expedition) with ventricular enlargement in the absence of elevated intracranial pressure, displaying clinical pictures with gait disturbance, mental deterioration, and incontinence, symptoms ever after referred to as the classic triad.

For the moment setting the feature of pressure aside, hydrocephalus as such (i.e. a condition characterised by excessive amounts of ñwaterò (Gr. ὕδωρ = hydor) in the head (L. cephalus, in turn from Gr. κεφαλή = kephalé) has attracted scientific interest since the days of Hippocrates (466-377 BC), who was probably the first to use the term in print (5). The early history of hydrocephalus treatment is marked by the enthusiasm and ingenuity of neuroscientific pioneers on the one hand, and the numerous deaths among patients shortly after exposure to their inventions, on the other. Valveless diversions of CSF (mostly from the ventricles, but at times from the cisterna magna or the lumbar region) into different low pressure compartments of the body (e.g. the subgaleal tissue, the jugular vein, the gallbladder, and the mastoid sinus, to mention a few) were used from the late 19th century. The development of antiobiotics and biocompatible and fatigue-free materials during the early 1900s and the construction of clinically successful valves (the first was introduced by Nulsen and Spitz in 1949) have turned the shunting of CSF of hydrocephalus patients into a considerably safer neurosurgical treatment. Nevertheless, a population-based survey of shunt complications (replacement, revision, removal, or exploration) in California during a period of 11 years (1990-2000), showed that adults treated with ventriculoperitoneal (VP) shunts (n=11 550) had a complication rate of 12% in the first month, 21% at one year, 27% at 5 years, and 29 % at 10 years, leading the authors to conclude that the current treatment is unsatisfactory for a large proportion of patients (6). In the European multicentre study presented in this thesis (study IV), the proportion of iNPH patients ï all treated with VP shunts and programmable valves ï requiring surgical interventions due to complications during the first year was 18% (26/141), close to the 21% at one year reported by Wu et al. (6). Similarly, in a recent prospective study from Gothenburg on perioperative risk factors during shunt insertion in adults (> 16 years old) covering a period of ten years, the proportion of shunt failures within 6 months was 18.9 % (85/450) (7).

Unsatisfactory as it may seem, letting the disorder run its course without intervening is rarely an acceptable alternative. On the other hand, the natural history of untreated iNPH has not been well studied, and it is not known whether iNPH is invariably progressive (8).

1.2. Idiopathic normal pressure hydrocephalus, a definition

Starting off with a recently proposed modest definition, hydrocephalus is an active (exit hydrocephalus ex vacuo) distension of the cerebral ventricles (exit benign intracranial hypertension or pseudotumor cerebri, and normal volume hydrocephalus) due to inadequate passage of CSF from its production sites to its point of absorption into the systemic circulation (9). For the classification of NPH, we need two additional groups of requirements, relating to communication between CSF spaces and to CSF pressure: There are open passages within the ventricular system and between the fourth ventricle and the subarachnoid space (SAS)(exit obstructions of the foramina of Monro, aqueductal

stenosis, fourth ventricle outlet block, and isolated fourth ventricle), and the intracranial pressure is within normal limits (exit choroid plexus papilloma and the majority of cases with secondary hydrocephalus). Finally, for the specific classification of iNPH, there is a requirement of an absence of identifiable antecedent causes (exit all cases of secondary hydrocephalus). This definition constitutes the basis for the diagnostic criteria for iNPH (10, 11), a subject we will turn to after a closer look at the most central of the features just presented, and the pathological changes associated with the condition.

1.2.1. Ventricular dilation

In adults the volume of the cavity enclosing the brain and the spinal cord is some 1500 ml (12). The total volume of CSF is approximately 190 ml. Out of these, some 38 ml reside within the ventricular system, 80 ml within the spinal subarachnoid space (sSAS) and the remaining 72 ml, or so, within the cranial subarachnoid space (cSAS)(13-15). The precise amount of CSF varies due to individual differences in absolute and relative sizes of the different CSF compartments.

An early and noteworthy effort to establish the shape and volume of the cerebral ventricles was made by Last and Tompsett (16), who, refining methods previously used by Leonardo da Vinci (17), Retzius (18), and Torkildsen (19)(among others), prepared casts of the ventricular systems of the brains of 24 adults aged 29-72, using Marco resin and loads of perseverance. They recorded several features of the casts, one of which was the ratio between the spread of the anterior horns and the width of brain, i.e. the Evansô index discussed later. They found the average capacity of the ventricles to be 22.4 ml (CI95% 16.5-28.3).

Aiming to improve the diagnostic possibilities of roentgenography, the neurosurgeon Walter Dandy introduced pneumoventriculography in 1918 (20) and, shortly thereafter, pneumoencephalography. One of the virtues of these methods was their ability to outline the cerebral ventricles. Since enlargement of the lateral ventricles was soon found to be the most frequent abnormality in encephalographic investigations, there was a need to find a suitable quantitative expression for ventricular size, and to determine its normal limits. For these purposes William Evans introduced the ratio of the distance between the tips of the frontal horns and the inner width of the skull (21). His preference of this ratio to the more simple measurement of the transverse diameter of the ventricles (as previously suggested by Davidoff and Dyke) was partly based on a calculation where Evans erroneously found the coefficient of variation to be smaller (and therefore better) for the ratio than for the diameter, whereas in fact the opposite was true (22). Nevertheless, so far the Evansô index (EI) has been the most extensively used estimate of ventricular volume. In the context of hydrocephalus a ventriculomegaly as evidenced by an EI $\geq$.30 or >.30 according to CT or MRI is often recommended or used as a diagnostic criterion (23-26), although a slightly larger quotient of $\geq$ .32 has also been advocated (27). A glance at the data from the casts of Last and Tompsett (16) shows that EI may occasionally be grossly misleading, and, hopefully, sufficiently automated pixel-based digital quantification methods will be able to replace it. In a recently published study (13) using such quantifications of magnetic resonance scans, the mean ventricular volume (VV) was 34 ml (sd 17) for women and 43 ml (sd 19) for men (with a sex-corrected mean of 38.5). The findings led the authors to suggest that a ventricular volume >77 ml or a relative ventricular volume (RVV, ventricular volume/total brain volume) > 4.96% should be used to define ventricular dilation in white elderly individuals. Mean values of VV

(and, more sporadically, RVV) of healthy individuals (HI) and patients with normal pressure hydrocephalus as reported in different volumetric studies are presented below.

Table 1. Ventricular volume (VV) and relative ventricular volume (RVV) in healthy individuals and in patients with normal pressure hydrocephalus

Ref	Healthy indivuals				Normal pressure hydrocephalus			
	n	Age[a]	VV	RVV	n	Age[a]	VV	RVV
Ambarki (13)	46	72 (60-82)	37 (18)	2.47 (1.2)				
Matsumae (28)	22	72 (61-80)	33 (10)	2.4 (0.6)				
Nestor (29)	152	76 (5)	38 (19)					
Kitagaki (30)					11	78 (5)	143 (34)	9.3 (2.1)
Palm (31)					26	75 (54-87)	156 (46)	
Tsunoda (32)	13	61 (53-79)	25 (10)		16	67 (47-84)	76 (19)	
Hiraoka (33)					21	76 (4)	124 (24)	

[a] The ages of the participants are presented as mean and (sd), or mean and (range).

As yet, the techniques applied in volumetric studies are too time consuming to be suitable for routine clinical settings. In the articles included in this thesis a ventricular distension as evidenced by an EI of $\geq$ 0.30 has been as used as a mandatory diagnostic criterion for iNPH.

1.2.2. CSF

CSF serves several functions. First, any object, wholly or partly immersed in a fluid is buoyed up by a force equal to the weight of the fluid displaced by the object. Hence, the effective weight of the brain is reduced from approximately 1500 g to 50 g. Rather than resting heavily on - and, in motion, being dragged across or bounced against - the bony surfaces of the inner skull, the brain floats, surrounded by a protective cushion. Secondly, CSF is involved in the regulation of intracranial pressure, a subject discussed later. Thirdly, the CSF produced within the ventricles communicates with the extracellular fluid (ECF) surrounding the neurons and glia, and thus indirectly regulates the composition of ECF. It thus has the potential to function as a sink for potentially harmful metabolites. Conversely, this free communication also gives CSF the potential to serve as a route for chemical messengers, e.g., neuroactive hormones, and nutrients.

1.2.2.1. Production

In human adults CSF is continuosly formed at a rate of approximately 500 ml per day or 20 ml per hour (34)(estimates of the exact rate vary between different methods of measurement). As indicated previously, CSF is a mixture of fluids from different sources, but most of it is produced by the choroid plexuses (CPs). The CPs are highly vascularised extensions of the pia mater that project into the ventricles through the roofs of the 3rd and 4th and the walls of the lateral ventricles. The CPs are branched and consist of numerous villi, each with a core of connective tissue and fenestrated capillaries (allowing the passage of ions, small molecules and fluids), and a cover of a single layer of cuboidal epithelial cells which is continuous with the ventricular wall. The blood supply to the CPs (in rats), has been found to be almost ten times greater than the cortical supply (35).

The formation of CSF is a two stage process; a passive filtration of fluid across the choroidal capillary endothelium and an active secretion across the epithelium.

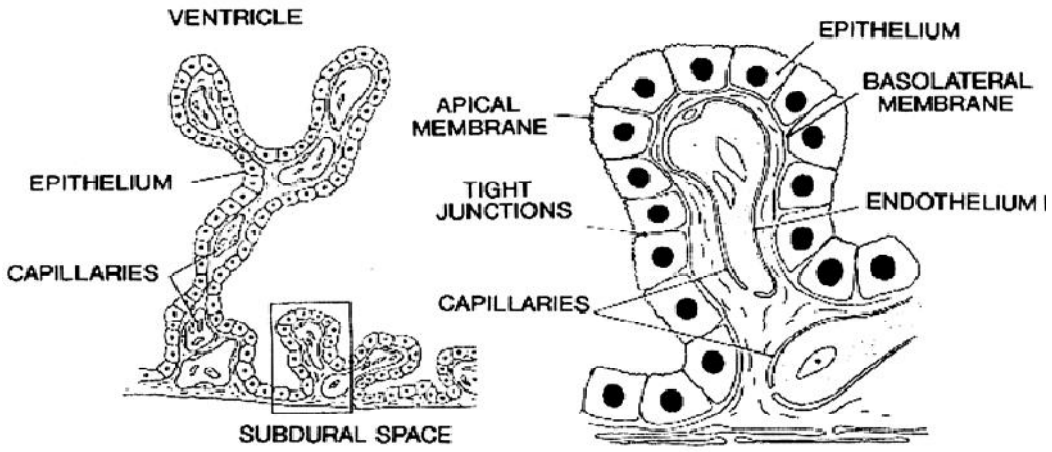

Figure 1. Morphology and ultrastructure of the choroid plexus. Left: The highly branched structure of the choroid plexus with villi projecting in to the ventricle. Right: The choroid plexuses consist of network of capillaries and connective tissue which is covered by a single layer of cuboidal epithelial cells. Reproduced with permission from Speake et al. (36).

The wall of the ventricles, the ependyma, is a membrane consisting of a single layer of cells ranging in type from low epithelial to cuboidal and columnar cells. The morphology of the walls is heterogenous and varies even within the same ventricle, e.g., regarding the presence/absence of ciliae, and the junctions between the ependymal cells, a feature that determines the extent of communication between the CSF and the ECF.

The CSF flows through the foramina of Monro, into the 3rd ventricle, continues through the aqueduct of Sylvius into the 4th ventricle, leaves the ventricular system and enters the subarachnoid space through the foramina of Luschka and the foramen of Magendie. From the cisterna magna the fluid passes into the sSAS and into the fossa interpeduncularis, around the brain stem and into the cisterna ambiens, forward into the cisternae cinereae terminales and upwards into cisterna corporis callosi. From the cisterns, CSF flows into the narrow subarachnoid spaces surrounding the cerebral and cerebellar cortices (14).

In HI the net flow of CSF follows the direction just presented, but the actual pattern of CSF motions is more complex and associated with the cardiac cycle. MR velocity imaging studies have made it possible to study CSF motion in relation to this rhythm. According to such investigations the pulsatile increase in blood volume causes the brain parenchyma to exert a compressive force on the ventricles that drives CSF out of the brain. A downward movement of the brain at the level of the corpus callosum, and a more pronounced downward movement of the brain stem, facilitates CSF flow into the sSAS as well as upwards, over the convexities, toward the sagittal sinus (14, 37). Later in the cardiac cycle, the direction of the flow is inverted, so that there is a cyclic to-and-fro movement of CSF and a corresponding pulsative mixing of CSF in the 4th ventricle, the basal cisterns and the upper sSAS (38).

The continuous secretion of CSF into the ventricles requires corresponding outflow mechanisms. Much of the discussion regarding such mechanisms has revolved around the question of whether there is a single (ñthe arachnocentric viewò), a dual (arachnoid and lymphatic), or perhaps an even more diversified system of CSF outflow (39).

1.2.2.2. Absorption

According to the most widely held view, the major escape route for CSF in man is through the arachnoid granulations. These were originally described by Antonio Pacchioni (1665-1726) in 1705 as ñpeculiar wartlike excrecencesò of the arachnoid, protruding into the lumina of the large dural sinuses. Luschka (40), some 150 years later, pointed out that these Pacchionian bodies were not ñpatologischen Bildungenò as believed earlier, but hypertrophied arachnoid villi, which are present in all brains, but generally microscopic in character (41).

Le Gros Clark (41) described the arachnoid villi as imperceptible (microscopic) at birth, but obvious at 18 months. The villi continue to develop with the greatest frequency in proximity to the superior sagittal sinus (SSS), so that ñé at the age of three they are disseminated over a considerable areaò (41). More recently, transmission electron microscopy investigations on newborn babies, have shown arachnoid granulations and occasional villi emerging in clusters from the floor of the lateral lacunae (supposedly remnants of the duplicated embryonic SSS), with the highest concentration close to the torcula (42). Moreover, the proliferations were found to be larger in two cases where ICP was suspected to be raised, an observation that fits well with a proposal of le Gros Clark, that the transformation from minute villi to full blown Pacchionian bodies is stimulated by the maturational increase of ICP (41). In adults, the majority of granulations have also been shown to project into the lateral lacunae (39, 43-45).

Late in life the arachnoid villi and granulations occlude and degenerate, along with a degeneration of the CPs. ñEventually the CSF circulatory system may fail, resulting in stagnation, contamination, compositional deficiencies, and impaired clearance of noxious substancesò (46).

In most vascularized tissues, lymphatic vessels are responsible for the collection of extracellular tissue fluids. The lymph is transported through channels and filtered through collections of lymph nodes, and then drained into the subclavian veins. There are no lymphatic vessels in the brain. In spite of this absence, when Key and Retzius (47) injected coloured gelatine into the cSAS of human cadavers, it subsequently appeared, not only in the arachnoid granulations, but also in the cervical lymph nodes. Reports from studies on several species, from mice to non-human primates, point to a direct communication between the perineural space of the cranial (especially the olfactory nerve) and spinal nerves and lymphatic vessels (39, 48-50).

In a study using radionuclide cisternography, Edsbagge et al. (38), showed that 38% of the CSF in individuals at rest (lying face-down), and 76% in physically active individuals (walking about between registrations) was absorbed from the spinal SAS, corresponding to an amount of 0.11-0.23 ml per minute (~7-14 ml per hour, ~160-330 ml per day. Spinal arachnoidal villi have been shown to exist in man (increasing in frequency from the cervical, via the thoracic to the lumbar region) and to have an intimate relationship with radicular veins (51). The reasons for the doubled absorption rate in the physically active individuals (i.e. upright as opposed to lying down) in the study by Edsbagge et al. (38)

could be the increased transvillus pressure gradient and/or an increased absorption through pressure dependent lymphatic pathways.

Finally, perivascular CSF transport or capillary absorption, may also play a role in normal as well as pathological states (52).

In patients with normal pressure hydrocephalus the net flow of CSF has been shown to be reversed, i.e., a larger quantity of CSF passes through the aqueduct heading for the supratentorial ventricles than in the opposite, outward direction (53, 54). The unavoidable conclusion of this finding is that patients with normal pressure hydrocephalus must have a transependymal route for CSF absorption. Further, the previously mentioned sink action of the CSF for ECF debris must be significantly attenuated, if not completely cancelled out.

1.2.2.3. ICP or CSF pressure

Pressure, per definition, is an effect that occurs when force is applied on a surface, and the SI unit for pressure is one newton per square meter, i.e., Pascal (Pa). However, since pressure is commonly measured by its ability to displace a column of liquid in a manometer, it is often expressed as the depth of a particular fluid, in the present context most commonly centimeters (or millimeters) of water (cmH_2O), or millimeters of mercury (mmHg). Examples of unit values and their equivalents are presented below (table 2).

Table 2. Pressure unit equivalents

kPa	mmHg	cmH2O
1	7.5	10.2
0.133	1	1.36
0.098	0.735	1

Intracranial pressure can be measured by different methods and in different CSF compartments, an intraventricular drain connected to an external pressure transducer being considered the golden standard (55). In most clinical settings, however, ICP estimates are derived from a lumbar spinal tap. Due to the dynamic nature of CSF pressure, instant measurements are considered potentially misleading. The normal pressures reported from the vignette cases could therefore be, and have been, regarded with some scepticism (56).

In health, ICP depends on the age and the posture of the subject. Resembling the conditions of a fluid column, a tilted or vertically oriented body will have an unevenly distributed CSF pressure. In an upright position ICP becomes increasingly negative (relative to the atmospheric pressure) from the level of the base of the neck and upwards (averaging ï 10 mmHg, ~ ï 14 cmH_2O, but never below ï 15 mmHg, ~ ï 20 cmH_2O (57), and increasingly positive along the spinal compartment.

In an adult in the recumbent position, the pressure at the level of foramina Monroi is normally 12-18 cmH_2O (~9-14 mmHg)(58). The pressure is lower in children (~4-10 cmH_2O), and lower still in term infants (~2-8 cmH_2O)(59). In a recent study, aimed to determine reference values for healthy elderly (n=40, aged 60-82) the median ICP, measured in a supine position, was 15.8 cmH_2O and the values corresponding to the 5^{th} and 95^{th} percentile were 10.6 and 19.4.

The lack of an agreed-upon upper threshold for normal ICP makes the validity of the designation ñnormal pressureò questionable. Acknowledging this conceptual deficiency, a group of European and American experts arrived at a consensus and placed the expected iNPH opening pressure between 6 and 24 cmH_2O (~4.4-17.6 mmHg)(60). When suggesting diagnostic criteria for iNPH, the same group recommended the similar but not

identical range of 5-18 mmHg (7-24.5 cmH_2O)(11). In the articles of this thesis, the upper limit for a diagnosis of iNPH was set to 18 mmHg, whereas no lower boundary was used.

1.2.2.4. CSF dynamics

Since the very definition of iNPH states that ñpressure is within normal limitsò, measurements of pressure per se are not very telling. Yet, there is an excess of CSF (ñactive distension of the ventriclesò, i.e. volume changes within the craniospinal chamber) and patients are improved by artificial diversion of the fluid (i.e., a substitute for the ñinadequate passage of CSF from its production sites to its point of absorptionò). Hence, it is the complex interplay between CSF production, absorption, volume and pressure, rather than pressure itself, which is of interest in the field of iNPH, and therefore measurements of the CSF dynamics, mainly by means of infusion methods, have a prominent role.

The craniospinal chamber has an *almost* fixed capacity. Accordingly, the sum of the volumes of tissue, CSF, arterial and venous blood is virtually constant, and any increase of the space occupied by one of these components will occur at the expense of the volume of one or more of the others. Due to the forces acting within the system, volumes and pressures will vary. The fundamental characteristic of the infusion methods is to challenge the system by altering the volume of CSF (by bolus injections (61), by constant rate infusion (62, 63), or by infusion at a rate that is adjusted in order to keep the pressure constant at predetermined levels (64)). The responses to these changes, in terms of pressure and flow, reveal the CSF dynamic properties of the system. More specifically, what is generally estimated is the resistance to outflow (R_{out}) or its reciprocal, the conductance (C_{out}), and the compliance or its reciprocal, the elastance.

In a recent study (65), the median R_{out} of healthy elderly was found to be 8.6 mmHg/ml/min, whereas the 90^{th} percentile was 17.4. In iNPH patients R_{out} is usually elevated (see e.g.,(66, 67)), but possibly less so when symptom duration exceeds two years (67). Albeit theoretically appealing (a most obvious contribution of a shunt system is a reduction of R_{out} to normal levels), the prognostic value of R_{out} is uncertain (see e.g., (68, 69)).

Lately, several reports from Norway have described the prognostic value of the cerebrospinal pulse pressure amplitude (similar to (reduced) compliance mentioned earlier, increased amplitudes reflect a poor compensatory reserve, i.e. a strained capacity to accommodate to volume changes)(70).

Summarizing the experiences of more than 2500 CSF infusion tests and 250 overnight ICP-monitoring sessions carried out with patients with hydrocephalus (47% with a diagnosis of iNPH) during a period of 17 years, Weerakkody et al. (52) conclude that there is no single variable in such measurements that allows definitive categorisation of CSF dynamics as normal or abnormal. ñAll parameters should be used collectively, with the understanding that between definitely normal and definitely disturbed CSF dynamics, there is a continuum of possible intermediate states which may produce different clinical responses to shunting, ventriculostomy or shunt revisionò(52).

1.3. Pathological changes

Several approaches have been used to study the pathological changes associated with hydrocephalus. This section is a short review of the findings.

1.3.1. Neuropathology

According to a review by del Bigio (71) the neuropathological changes associated with hydrocephalus in humans can be summarized as follows: The ependyma may be normal, stretched, torn, or totally destroyed. Anecdotal reports have described epithelial atrophy and stromal sclerosis of the CPs. In the subependymal region there is frequently a periventricular reactive gliosis. Periventricular oedema is a frequent finding and the extracellular spaces in white matter adjacent to the ventricles are enlarged. There is a reduced density of capillaries in the corpus callosum, and a reduced quantity and caliber of capillaries in the periventricular grey and white matter. There is also a thinning of the corpus callosum and a compression of the periventricular white matter. There is axonal degeneration and a loss of axons in long standing hydrocephalus. Descending degenerative changes have been observed in the corticospinal tracts of the human spinal cord. Secondary loss of myelin has been reported, suggested to be caused by oedema. Axonal damage is probably frequent, due to axonal stretching and vascular changes causing chronic ischemia and anaerobic glycolysis. The cerebral cortex is distented and thinned and gross atrophy of the basal ganglia has been reported. Vacuolization and degeneration of neurons in the hippocampal formation have been observed.

There are also findings implying an association between a prolonged hydrocephalic state and the development of neurofibrillary tangles in neurons of the cortex, the hippocampus, and the brain stem. In conjunction with bulging of the tuber cinereum and widening of the third ventricle, vague neuronal irregularities and pyknosis (nuclear shrinkage in dying cells) have been described in various hypothalamic nuclei, but these reports are not well substantiated (71).

1.3.2. CSF biomarkers

There is an ongoing search for CSF biomarkers for iNPH. Admittedly, several studies have compared patients with NPH to controls, but the general impression is that the major contribution to the reported deviations stem from patients with secondary NPH. In the last few years, investigators have begun to report results for iNPH patients separately, but so far the studies are scarce. Tullberg et al. (72) determined the CSF concentrations of the major monoamine metabolites (HVA, 5-HIAA and HMPG), sulphatide (a marker for demyelination, that distinguishes between NPH and subcortical arteriosclerotic encelopathy (SAE)(73)), ganglioside GD3 (a marker for gliosis), Tau protein and neurofilament light protein (NFL)(both markers for neuronal degeneration), finding a pathological deviance from normal reference values only for NFL. Interestingly, this elevation, presumed to indicate periventricular neuronal dysfunction, was found to correlate with preoperative functional status. Correspondingly, the decrease in NFL following treatment was correlated with the degree of clinical improvement.

Ågren-Wilsson et al. (74), comparing iNPH to HI and to patients with SAE, found NFL to be increased in both iNPH and SAE. The concentrations of total tau, phospho-tau and Aβ42 (markers associated with Alzheimer disease (AD)) were significantly lower in the group of iNPH patients than in the comparison groups. Kapaki et al. (75), comparing groups of HI, iNPH and AD patients, found equally decreased levels of Aβ42 iNPH and AD patients (both significantly lower than in HI). Unlike the previously mentioned studies, however, Kapaki et al. also found the concentration of total tau to be significantly increased in iNPH, although not as much as in AD. Phospo-tau was increased in AD as expected, but normal in iNPH (other markers were not investigated).

1.3.3. Structural imaging

The importance of structural imaging in the investigations of a disorder that is partly defined by ventricular dilation is self-evident. However, there are features besides the ventriculomegaly that are worth noting. Due to the active nature of the distension of the ventricles, there is frequently a suprasylvian outward-upward shift of the brain, causing a marked tightness of the high-convexity and the medial parietal subarachnoid spaces. Frequently, there is also a widening of the Sylvian fissures. The callosal angle (on coronal sections) is often acute in iNPH, a feature that has been shown to separate iNPH patients from patients with AD and HI (76).

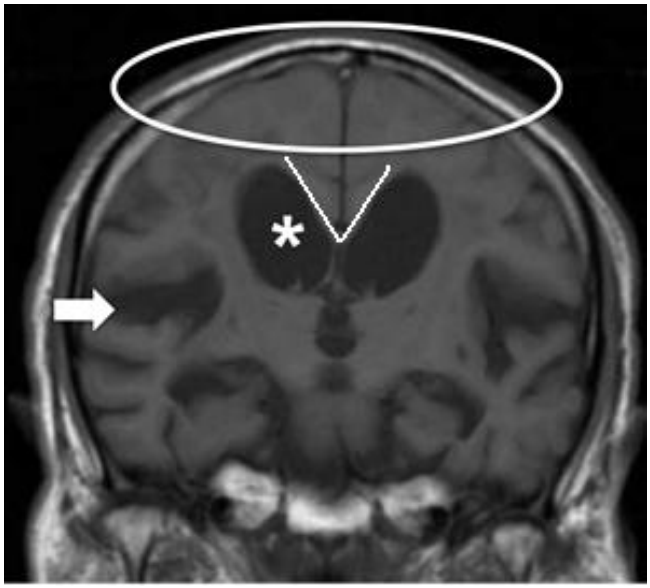

Figure 2. Coronal T1-weighted MR-image of a patient with iNPH showing ventricular enlargement (*), high convexity tightness with obliterated convexity sulci and medial tightness (oval ring), expanded Sylvian fissures (arrow), and acute callosal angle. Modified and reproduced with permission from Hashimoto et al. (77), with the authorôs addition of the high-lighted callosal angle.

Changes associated with periventricular oedema and white matter ischemia (periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH)) are also frequently seen in iNPH patients. In a mixed NPH sample (sNPH, n=21 and iNPH, n=13) Tullberg et al. (78) found DWMH in no less than 73% of the patients. Importantly, neither risk factors for cerebrovascular disease, nor the presence of DWMH were found to have a negative impact on the outcome of shunt surgery.

In a subsequent attempt to identify white matter changes that could discriminate between NPH patients (n=29) and patients with Binswangerôs disease (BD, n=17), no such distinguishing changes were found, despite rigid diagnostic criteria (79). A possible explanation for this, as argued by Tullberg et al. (79), could be that the two disorders form a pathophysiological continuum of increasing microangiopathy.

1.3.4. Functional imaging

A variety of techniques have been utilized to study the cerebral blood flow changes associated with NPH. Reviewing the literature in 2001, Owler et al. (80), found previous studies of CBF in NPH to be inconclusive. Most studies at that stage, however, did point

to a global reduction of CBF. In those studies where regional differences were observed between patients and controls, these were most likely to be found in the frontal region. Although some investigators found global CBF to be lower in NPH in comparison to cortical atrophy or Alzheimerôs disease, most investigators were unable to find such differences. Evaluations of the prognostic value of CBF measurements also pointed in different directions, with low preoperative CBF found to be beneficial by some, high by others, and some, again, finding neither a prognostic value in preoperative CBF nor any significant differences between pre- and postoperative measurements despite clinical changes.

Later Owler et al. (81) conducted a study that was technically superior to most of the studies they had previously reviewed, now using positron emission tomography (PET) and MR coregistration. Differences between HI (n=12) and iNPH patients (n=11) were found in the cerebrum and in the cerebellum. No differences were found for regions in white matter, but there were marked differences in deep grey matter; the thalamus, the head of the caudate nucleus, and the putamen.

Klinge et al., in a retrospective analysis of PET results in 65 patients with iNPH (82), found blood flow reductions in anterior and basal mesial frontal regions, and in a smaller anterior temporal area. Importantly, these reductions were correlated with preoperative functional impairment, and postoperative functional changes were paralleled by increased flow in superior mesial frontal regions.

Momjian et al (83), investigated the peri- and paraventricular CBF with PET in 12 iNPH patients during a controlled rise in ICP. Ten HI served as controls for the baseline values. The global mean baseline CBF of iNPH patients was significantly lower than that of HI. In iNPH patients regional CBF increased with the distance from the ventricles, whereas there was no such pattern among HI. The rise in ICP and an associated decrease in cerebral perfusion pressure (CPP=mean arterial blood pressure-ICP, i.e., the pressure gradient acting across the cerebrovascular bed), caused a further reduction of CBF that was most pronounced in the paraventricular watershed region.

1.4. The diagnosis and treatment of iNPH

A very influential supplement was published in Neurosurgery in 2005, the iNPH guidelines. It is the product of the joint efforts of several American and European researchers, compiled by a study group led by Anthony Marmarou (1934-2010), ñto establish a firm baseline as to where we are with regard to our ability to accurately diagnose and manage the iNPH patientò(84)(p i). Preliminary versions were reviewed by European and Asian collegues and further refined by the study group after receiving this feedback. The guidelines cover four major topics, the clinical diagnosis of iNPH (11), the value of supplementary test (60), surgical management (8), and outcome assessment (85). To avoid confusion, in what follows, these guidelines will be referred to as the American-European (AE) guidelines, as opposed to the Japanese counterpart presented later.

1.4.1. Diagnostic criteria according to American-European guidelines

Acknowledging the fact that the degree of diagnostic certainty varies, three different designations are used; ñprobableò, ñpossibleò, and ñimprobableò. The former two, (table 3, next page), are based on history and clinical findings, brain imaging, and physiological data.

Table 3. Diagnostic criteria for iNPH according to the American-European guidelines.

Clinical history

Probable iNPH	***Possible iNPH***
Reported symptoms **must**	Reported symptoms **may**
have an insidious onset	have a subacute or indeterminate onset
begin after age 40 yr	begin at any age after childhood
have a duration of at least 3 to 6 mo	have lasted less than 3 mo or indeterminately
evolve in the absence of antecedent events known to cause sNPH	follow events such as mild head trauma, remote history of intracerebral hemorrhage, or childhood and adolescent meningitis or other conditions that are judged not likely to be causally related
be progressive over time	be nonprogressive or not clearly progressive
appear in the absence of other conditions sufficent to explain them	coexist with other disorders, but not be entirely attributable to these conditions

Clinical findings

Probable iNPH	***Possible iNPH***
Gait/balance disturbance (mandatory) combined with either or both of impaired cognition and urinary disturbance	Incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance, alternatively; gait disturbance or dementia alone
The gait /balance disturbance should have at least two of the following features 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 f. Retropulsion (spontaneous or provoked) g. *En bloc* turning ($\geq$ 3 steps for 180°) h. Impaired walking balance, as evidenced by two or more corrections out of eight steps on tandem gait testing	
Cognitive impairment Documented impairment or decrease in performance on screening instrument or at least two of the following: a. Psychomotor slowing b. Decreased fine motor speed c. Decreased fine motor accuracy d. Difficulty dividing or maintaining attention e. Impaired recall, 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

Urinary incontinence, with either of
a. Episodic or persistent urinary incontinence not attributable to primary urological disorders
b. Persistent urinary incontinence

Imaging

Probable iNPH	***Possible iNPH***
EI > 0.30 No obstruction to CSF flow One of the following supportive features 1. Enlargement of temporal horns not entirely attributable to hippocampus atrophy 2. Callosal angle of 40 degrees or more 3. Altered periventricular water content not attributable to microvascular ischemic changes or demyelination 4. Flow void in aqueduct or 4^{th} ventricle	EI > 0.30 No obstruction to CSF flow Cerebral atrophy potentially explaining ventricular size is accepted Structural lesions that may influence ventricular size are accepted

Physiological data

Probable iNPH	***Possible iNPH***
CSF opening pressure of 5ï 18 mm Hg (or 70ï 245 mm H_2O) 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.	Opening pressure measurement not available or pressure outside the range required for probable INPH.

A diagnosis of Improbable or Unlikely iNPH is given when
1. There is no evidence of ventriculomegaly
2. There are signs of increased intracranial pressure, such as papilledema
3. No component of the clinical triad of INPH is present
4. Symptoms are explained by other causes (e.g., spinal stenosis)

The AE guidelines also suggest the use of outcome signifiers, namely Shuntresponsive iNPH and Shunt-nonresponsive iNPH. Admittedly, the proportion of probable iNPH patients improving after shunt surgery may be expected to exceed the corresponding proportion of improbable iNPH patients. The terms Shunt-responsive and Shunt-nonresponsive, however, have nothing to do with expectations, and should be applied independently of diagnostic category. Thus, they should be considered as postsurgery specifications that are to be added to each of the three diagnostic categories.

1.4.2. Diagnostic criteria according to Japanese guidelines

The Japanese Society of Normal Pressure Hydrocephalus begun developing evidence based iNPH guidelines in February 2002, and had them published in Japanese two years later. A short summary in English was also published in 2004 (86), whereas a complete English version was published in 2008 (10).

In the Japanese guidelines cases are classified as probable or possible, i.e., the same labels as in the AE guidelines, but there is third category of definite iNPH, intented for patients whose symptoms improve after treatment. Further, the categories are hierarchically ordered in the sense that a diagnosis of definite iNPH is attainable only if the criteria for probable iNPH have been fulfilled, and, in turn, a diagnosis of probable iNPH is attainable only if the criteria for possible iNPH are fulfilled. The diagnostic criteria of the Japanese guidelines are listed in table 4.

Table 4. Diagnostic criteria according to the Japanese guidelines, grouped under the same headings as in table 3.

Clinical history

Possible iNPH	***Supplementary notes***
Begins after the age of 60	Symptoms are slowly progressive; however, sometimes an undulating course, including temporal discontinuation of development and exacerbation, is observed.
Clinical symptoms cannot be completely explained by other diseases	Other neurological diseases including Parkinsonôs disease, Alzheimerôs disease. and cerebrovascular diseases may coexist; however, all such diseases should be mild.
Preceding diseases possibly causing ventricular dilation are not obvious	

Clinical findings

Possible iNPH	***Supplementary notes***
More than one of the clinical triad.	Gait with small stride, shuffle, instability in walking, and increase of instability on turning.

Imaging

Possible iNPH	***Supplementary notes***
EI > 0.30	Narrowing of sulci and subarachnoid spaces over the high convexity and midline surface, and dilation of the sylvian fissure and basal cistern are often observed. Periventricular changes are not essential. CBF is useful for differentiation

Physiological data

Possible iNPH	***Supplementary notes***
CSF pressure of 200 mmH_20 or less Normal CSF content (visual inspection)	None

Probable iNPH	***Supplementary notes***
1. Fulfill criteria for possible iNPH 2. One of the following: a. Improvement after CSF tap test b. Improvement after CSF drainage c. Abnormal R_{out} and ICP monitoring	None

Definite iNPH	***Supplementary notes***
1. Fulfilled criteria for probable iNPH 2. Improvement after shunt insertion	None

1.4.3. A comparison between the two sets of criteria

The main differences between the AE and the Japanese criteria are the following: Individuals aged 40-60 years and individuals with CSF pressures of 20-24.5 may be diagnosed as iNPH according to the AE criteria, but not according to the Japanese criteria. The category of improbable iNPH is unique to AE guidelines, whereas definite iNPH is unique to the Japanese guidelines. It is important to note that in the AE guidelines the treatment outcome is described (Shunt-responsive or Shunt-nonresponsive iNPH) independently of diagnostic category, whereas, in the Japanese guidelines, outcome is regarded as the key to whether the preoperative diagnosis was true or false, as shown by the term ñdefiniteò.

The Japanese criteria require positive findings on supplemental tests for the diagnosis of Probable iNPH, whereas the AE criteria do not. Most importantly, according to the Japanese guidelines, ñthe shunt procedure is indicated for Probable iNPH, not for Possible iNPHò, whereas the AE guidelines would permit consideration of shunt treatment even for patients with Improbable iNPH.

The practical implications of these differences are hard to evaluate. Comparisons between studies utilizing different guidelines will inevitably be fraught with translational ambiguities. The situation is far better than before the advent of the two sets of guidelines, but one would have been better.

1.4.4. Treatment

The most common treatment for iNPH is diversion of CSF through a ventriculo-peritoneal (VP) shunt (87, 88). A wide variety of shunt systems are available. The core requirement is the establishment of an operative pressure differential, allowing escape through the valve whenever CSF pressure reaches a predetermined level. In an upright position, the hydrostatic forces in the shunt system will cause overdrainage (ñsiphonageò). Hence, it is now customary to add an anti-siphon device, immediately distal to the valve, to prevent gravity dependent drainage. However, counteracting siphonage may render shunt treatment less effective in some cases of iNPH (89).

1.5. Epidemiology

Studies exploring the prevalence and incidence of iNPH have come to varying results, due to the use of different diagnostic criteria and different investigational approaches. In a recent study, using the criteria for probable and possible iNPH presented in the AE guidelines (11), Brean et al. found prevalences of 21.9/100 000 (probable) and 28.7/100 000 (possible) and incidences of 5.5/100 000 and 7.3/100 000 per year (90). The study was not truly population based (patients were actively sought and recruited from a population of 220 000 Norwegians), why the estimates are to be regarded as minima. Two Japanese studies have reported substantially higher prevalence estimates of 1.4 % (91) and 2.9 % (92)(i.e., more than 100-fold that of the Norweigan study). Both of these studies used randomly selected but small samples from populations of community dwelling individuals aged 65 or more. The patients were diagnosed retrospectively with criteria requiring only positive findings on MRI and one of the triad symptoms.

Two Scandinavian studies have reported on the annual frequency of neurosurgical treatment of patients with iNPH. In Sweden the average was 0.92 cases per 100 000 inhabitants per year during 1996-1998 (88). Similarly, in Norway the rate was 1.1/100 000/year during 2002-2006. A comparison even with the modest estimate of the incidence of iNPH (5.5/100 000/year) shows that only a minority of the patients receive treatment.

1.6. Signs and symptoms

The first systematic study of the symptoms attributable to ñoccultò hydrocephalus was done by Fisher (93) and based on a retrospective analysis of 30 patients treated at the Massachusetts General Hospital from 1959 to 1977 (selected out of a total of 60 patients, on grounds that are not clarified). Earlier descriptions had already identified the triad, why particular attention was now paid to its constituents. Other symptoms, however, were also sought for, and negative clinical characteristics were noted. In the following paragraphs the hydrocephalic gait, balance, and incontinence problems are presented briefly, commencing with the findings of Fisher, followed by a somewhat lengthier review of findings pertainng to neuropsychological changes.

1.6.1. Gait and other motor symptoms

In the study by Fisher (93), all of the 16 patients who showed a definite improvement after shunting had a gait disorder prior to surgery. In 12 of them gait was the earliest symptom. In three cases gait and mentation began to change at about the same time. In one single case mental changes were the first to be noticed, and this patient was suspected to suffer from AD. Among the 11 patients in whom shunting was ineffective, mental symptoms appeared first in nine (two of whom had no gait disturbance at all, whereas six had a gait disturbance that was rated as slight), and together with gait in one. Gait disturbance was the first symptom in only one patient of those who showed no response to shunting (93). Judging from these data, gait disturbance appears to be the predominant symptom, and most often the first to be noted among patients who are improved by shunt surgery. It has also been shown that gait disturbance is the main complaint in the majority of iNPH patients (86%) and their relatives (75%)(94).

Stolze et al. (95) examined the hypokinetic gait of iNPH patients (n=10) in detail, in comparison to the gait of healthy controls (n=12), and found it to consist of a triad of reduced stride length (with a considerable variability from step to step), reduced foot-to-floor clearance (accompanied by a loss of the normal dorsal extension in the terminal

swing phase), and a disturbance of the dynamic equilibrium (marked by an increased step width - with a less than normal variability from step to step - and an abnormal outward rotation of the feet). Freezing of gait was seen in three of the patients.

Following a tap test (removal of 30 ml of CSF) the greatest improvement was seen in velocity, followed by stride length, double-limb support phase, stance phase, and the swing phase (95).

A study comparing iNPH patients (n=11) to patients with Parkinsonôs disease (n=10)(96), showed the increased step width with reduced variability, the outward rotation, and the reduced foot-to-floor clearance to be iNPH specific. The feature of reduced velocity due to a diminished and highly variable stride length, was common to the two diagnostic entities. Visual and auditory ques were somewhat more effective for patients with Parkinsonôs disease, but had an impact in iNPH as well.

The findings of the studies referred above, indicate that deficits in two different functional systems contribute to the iNPH gait disturbance; a motor system and a balance regulating system. The former of these systems, in turn, can also be subdivided, since the motor part of locomotion has been found to rely on two functional networks, an executive network for steady state walking, and a planning network for the planning and modulation of locomotion (97) (figure 3).

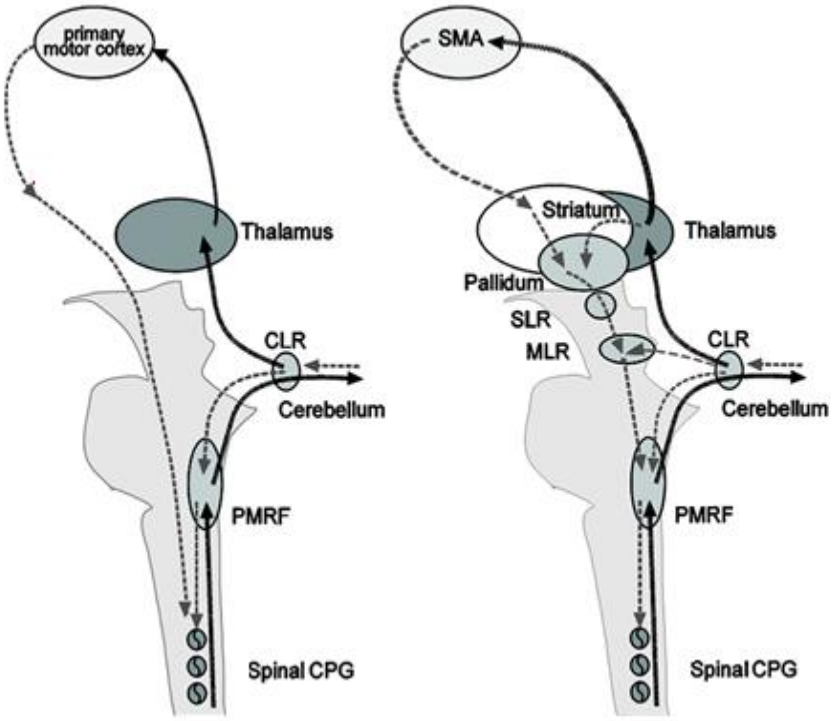

Figure 3. The ñexecutiveò (left) and the ñplanningò network of locomotion. Execution of steady-state locomotion goes from the primary motor cortex areas directly to the spinal central pattern generators (CPG), bypassing the basal ganglia and the brainstem locomotor centers. There is also a spinal cord-cerebellar-thalamo-cortical feed-back loop. For planning and modulation of locomotion cortical locomotor signals originate in the prefrontal supplementary motor areas (SMA) and are transmitted through the basal ganglia via disinhibition of the subthalamic locomotor region (SLR) and the mesencephalic locomotor region (MLR) where they converge with cerebellar signals from the cerebellar locomotor region (CLR). The MLR functionally represents a crosspoint for motor information from basal ganglia and cerebellar loops. Descending projections are directed to the medullary and pontine reticular formations (PMRF) and the spinal cord, ascending projections are in the main part concentrated on the basal ganglia and the nonspecific nuclei of the thalamus (not shown for sake of clarity). The CLR also projects via the thalamus back to the cortex. Cortical signals are furthermore modulated via a thalamo-cortical-basal ganglia circuit.
From la Fougere et al. (97), reproduced with permission.

The gait disorder in iNPH may stem from compression, deformation or subcortical white matter changes affecting upper motor neuron fibres passing through the medial portion of the corona radiata. However, electromyographic studies have pointed to disturbances of the phased muscular activation, indicating a deficient subcortical motor control, rather than, or in addition to, a pyramidal tract disorder (11).

Palm et al. (98) examined the relationship between gait (but also cognition and bladder function) and ventricular volume (relative to sulcal volume) in infarct-free participants in the population based Age, Gene/Environment Susceptibilityï Reykjavik Study (n=858), and found gait (and cognition) to be inversely related to relative ventricular dilation.

De Laat et al. (99) approached the problem of gait from a different angle, examining instead the influence of loss of white matter integrity by diffusion tensor imaging in patients with small vessel disease (n=429). Gait disturbances were found to be attributable to loss of integrity of multiple white matter fibres connecting different cortical and subcortical regions, mediating intra-, and, particularly, interhemispheric integration of motor and sensory signals. A striking feature of the study, from the iNPH perspective, is the close proximity of the ventricles to the tracts found to be linked to gait velocity, stride length and stride width.

A few authors have supplemented the assessment of gait in iNPH with examinations or tests of other motor functions. In a study by Blomsterwall et al. (100) the abilities to turn from side to side in bed, to rise from a supine to a sitting position, to extend and flex a knee repeatedly while sitting on a chair, to move a hand back and forth from knee to chin, and, similarly, to move the hand from the knee to point at the nose with the index finger, were all improved following a CSF-tap test and after three months of shunt treatment. Krauss et al. (101) noted that the majority (74%) of iNPH patients (n=65) had akinetic symptoms in the upper extremities (brady- and hypokinesia) and/or the face (hypomimia). More recently, detailed investigations of the motor function of the hand while grasping and lifting an object revealed similar hypokinetic patterns in patients with iNPH and Parkinsonôs disease in contrast to HI (102). Further, application of objective methods to capture upper limb extrapyramidal signs, revealed prolonged reaction and movement times and increased resting tone in iNPH patients, as well as increased difficulties in self-initiated tasks in comparison to stimulus-cued tasks (103).

1.6.2. Balance and posture

Imbalance and postural dysfunction are common symptoms in iNPH, and strongly associated with the gait difficulties. Assessments using a force platform revealed that NPH patients had a larger displacement of the centre of pressure in the forward-backward direction, a larger sway area, a higher backward velocity and a more neutral or forwardly directed inclination than HI (104). A frequently observed and subjectively reported characteristic of the postural dysfunction and balance problems of iNPH patients is a tendency to lean and/or fall backwards, a propensity that has been found to be associated with an abnormal subjective visual vertical in pitch (26).

1.6.3. Incontinence

Recalling the Fisher study (93), 10 of the 16 successfully treated patients experienced some degree of urinary incontinence. Incontinence is the least well characterised symptom of iNPH. It is usually reported to develop later than the symptoms of gait and neuropsychology. However, problems with urgency and increased frequency of urination

appear early in some patients, yet not at all in others (cf. study IV where 13% of the patients had no urgency or incontinence). Similarly, some patients, describe an almost instant relief of problems of incontinence or urgency after surgery, whereas others experience no change despite marked improvement in other areas of functioning.

Micturition is subjected to voluntarily control by means of a complex and widely distributed circuitry and is thereby vulnerable to CNS disorders, but also to normal age associated changes. The most firmly established components of the circuitry are the periaqueductal grey (PAG, receiving bladder afferents from the spinal cord), the insula (especially in the right hemisphere, an area related to visceral sensations), and the anterior cingulate cortex. Further, the prefrontal cortex (especially the medial region) is involved in decisions on whether to void or not. Once voluntary voiding is commenced, there is an ensuing activation of the genu of the cingulate gyrus, and the pontine micturation centre (PMC).

1.6.4. The neuropsychology of iNPH, manifest symptoms

The mental changes of patients with iNPH are often denoted as ñdementiaò. Dementia, however, is a broad concept, embracing a variety of neuropsychological, i.e., cognitive, conative, emotional and behavioral manifestations. The concept also indicates a rather advanced stage of deterioration not always reached by iNPH patients, where mean values on one of the most utilized cognitive screening instruments, the minimental state examination (MMSE, (105)) for studied samples generally hover around 25.

More elaborate descriptions of the mental changes associated with NPH mostly stem from observations of mixed samples (i.e., idiopathic and secondary cases). These descriptions either point to what Meier et al. called the ñmultifariousness of clinical manifestationsò (106), or try to capture the gist of the state by enumerations of conspicuous and recurring symptoms. Thus, Merten (107) mentions reduced drive, loss of interest and activity, emotional indifference, and loss of spontaneity, while others have stressed inattention, paucity of thought, forgetfulness, diminished intellectual agility, apathy, psychomotor slowing and executive deficits (e.g. (108, 109)). The symptomatology is at times dominated by an apparent tiredness or drowsiness with frequent yawns and, sometimes, hypophonic, slow and even slurred speech, and a corresponding dampening of all mental and motor processes (often accompanied by reports of increased need of daytime sleep and a pronounced tendency to fall asleep whenever passive). Confusional states, with incoherent thinking and speech, disorientation, delusions and hallucinations, or amnesia combined with confabulations – equivalent to the Korsakoff psychosis are also, but less frequently, seen. Further, symptoms frequently associated with stroke or traumatic brain injuries, such as fatigue or reduced mental endurance, concentration and memory difficulties, emotional instability and irritability (110, 111) are often conveyed by patients with iNPH.

1.6.4.1. Classification of organic psychiatric disorders

Aiming to bring order into the plethora of symptoms facing professionals in the fields of neurosurgery and neurology, Lindqvist and Malmgren (112), recognizing that available diagnostic systems were partly illogical and inadequate for such purposes, introduced a system for classification of organic psychiatric disorders (OPDs)(113, 114).

This system, the LM-system, describes six major OPDs which are identified through the presence of clusters of symptoms. Importantly, although the disorders bear names that,

in part, include some of the symptoms associated with them, they are not identical to the different clusters. Instead, they represent hypothetical pathogenetic processes, which are to be conceived as being situated on a level between manifest symptoms (cf. previous section) and distal etiology.

One of the tenets of the psychophysiological theory behind the LM-system is the conception of the brain as an adaptive system that tends to behave convergently, i.e., reacting in a restricted number of ways to many different etiological conditions. Conversely, different individualsô brains subjected to similar etiological conditions, may react divergently. The recognition of these facts, the tendencies of convergence and divergence, renders the LM-system, by empirical necessity, largely independent visavi localisational and nosological determinations. Another important feature of the classification system is that it acknowledges the possible simultaneous occurrence of several OPDs, even when the symptoms associated with one of them are too prominent to allow the actual observation of any of the symptoms of the others (which is often the case).

The hypothetic pathogenetic processes are fairly stable over time, and they often have a considerable prognostic value (this, however, is anything but independent of etiology).

The six major OPDs (and their associated symptoms) are the Astheno-Emotional Disorder (AED; concentration and memory difficulties, fatigue, irritability and/or emotional lability), Emotional-Motivational Blunting Disorder (EMD; apathy, emotional indifference, lack of drive), Somnolence-Sopor-Coma Disorder (SSCD; impaired wakefulness, general slowing and dampening of cognitive, emotional, conative and motor processes), Confusional Disorder (CD; incoherence, disorientation, memory encoding deficits, delusions and/or hallucinations, at times agitation), Korsakov-Amnestic Disorder (KAD; profound memory deficits, confabulations), and Hallucination-Coenestopathy-Depersonalisation Disorder (HCDD; visuo-perceptual disturbances, visual pseudohallucinations, bodily pseudohallucinations, depersonalisation and/or derealisation).

According to the LM-system then, these are the organic psychiatric reactions that can be expected to be seen most frequently in patients within a geroneuropsychiatric, neurological or neurosurgical context. The prognostic value was mentioned earlier; another benefit of the system is that it accomplishes a narrowing down of what might otherwise seem like an endless quantity of combinations of manifest symptoms. Thus, yet another important merit is its ability to facilitate communication between those who are involved in each specific case.

The classification of OPDs and its prognostic importance has been described in mixed samples (115, 116). At the Hydrocephalus research unit the the LM-system is put to daily use in the clinical investigations of iNPH patients, and studies are underway, eventually providing a more comprehensive discussion on pathogenesis.

As yet, data and clinical experience show that the overwhelming majority of iNPH patients initially exhibit symptoms indicating AED, soon followed by the development of EM and/or SSCD. Simultaneous occurences are common, with the SSCD being most amenable to treatment, followed by EMD, whereas AED is more resilient. Patients with iNPH seldom develop CD, KAD or HCDD. If so, there is reason to suspect significant contributions of other distal etiologies, and the prognostic expectations should be tempered accordingly.

1.6.4.2. Neuropsychological impairment and change

Organic psychiatric disorders influence and set limits to what patients can accomplish on neuropsychological tests and mold the quality of their performance. These relationships await scientific scrutiny.

The studies investigating neuropsychological performance in pure iNPH samples are scarce, and there is no concensus on which tests should be used, nor are there any agreed upon standards for the definitions of impairment or change. What follows is an account of what has been found at baseline and at follow up examinations in recently published reports.

Iddon et al. (109) divided their sample of iNPH patients (N=11) into two subgroups of demented (n=5) and non-demented patients on the basis of their preoperative results on the MMSE, defining dementia as equivalent to obtaining scores < 24. The subgroups were subjected to different test batteries, since the authors were specifically interested in the characteristics of deficits in mildly affected patients. For the demented patients only results on the MMSE and the Kendrick object learning test (KOLT, (117)) were reported. Despite extremely poor preoperative results (the mean MMSE score before surgery was 10.4, with two of the patients achieving scores of 5 points (!)), they were all considered non-demented after six months of shunt treatment. The KOLT scores were also well below the non-dementia-limit of the test preoperatively, but fell in the normal range after treatment. The non-demented patients were, apart from the MMSE and the KOLT, also tested with two verbal fluency tasks and tests included in the Cambridge neuropsychological test automated battery (CANTAB, (118)). It was concluded that these mildly affected iNPH patients showed executive deficits. Further, since these deficits remained after treatment, in contrast to quite severe dementia, they were presumed to be non-reversible.

A larger sample of iNPH patients (N=42) was studied by Thomas et al. (119), who used subtests of the Wechsler Memory Scale (WMS, (120)) tapping immediate and delayed verbal recall, Rey-Osterrieth Complex Figure (ROCF; copy and delayed recall (121)), Rey Auditory Verbal Learning Test (RAVLT, (122)), a line-tracing task (123), Trailmaking test B (124), and the Stroop Colour-Word Test (125). The authors defined impaired preoperative performance as equivalent to obtaining scores falling more than 1 sd below the mean for demographically comparable individuals, according to published norms for the different tests. With this definition the proportions of iNPH patients scoring in the impaired range on the different tests varied as shown below (table 5).

Table 5. Proportions of iNPH patients scoring more than one sd below normative mean.

Thomas et al. (n=42) (119)	
Neuropsychological test	*% performing below 1 sd*
RAVLT delayed recall	76
Stroop Color-Word	76
Trail making B	62
RAVLT total	59
WMS delayed recall	56
WMS immediate recall	49
ROCF delayed recall	41
Line-Tracing	32
ROCF direct copy	32

The authors defined significant improvement in a subtest as a positive change of at least 1 sd for the patientôs age, sex and educational level. Significant improvement in overall neuropsychological outcome was defined as a 4-point improvement in MMSE, or an improvement by 1 sd in 50% of the administered subtests. Fifty-two percent (22/42) of the patients were improved.

The same definition had been used in a previous study by Duinkerke et al. (126) who found 60% (6/10) of their iNPH patients to be improved, and it was subsequently applied in a study by Foss et al. (127), as well as in study II, yielding proportions of 44% (12/27) and 51% (24/47). An interesting finding in the study by Foss et al. (127), was that those who responded neuropsychologically favourably to shunt treatment, i.e., according to the definition, had a significantly higher mean ICP wave amplitude (cf. section 1.2.2.4) according to analyses of continuous monitoring.

Ogino et al. (128) compared 21 iNPH patients to 42 patients with Alzheimerôs disease (AD). Each iNPH patient was matched to two AD patients on the basis of age, sex and MMSE score. The instruments used were the Orientation and Construction tasks of the Alzheimer Disease Assessment scale (ADAS, (129)), the complete revised version of the WMS (WMS-R, (130)) and the complete revised version of the Wechsler Adult intelligence scale (WAIS-R, Pearson Education, Upper Saddle River, New Jersey). INPH patients had significantly higher scores on the Orientation task of the ADAS, on the General memory and Delayed recall of the WMS-R, but scored significantly lower on the Attention/concentration tasks of the WMS-R, and the Digit span, Arithmetic, Block design and Digit symbol substitution subtests of the WAIS-R. In the comparison of composite scores of the WAIS-R, the groups were equal with regard to the verbal IQ, whereas patients with iNPH had significantly lower performance IQ.

The authors summarized their findings by stating that, in comparison to patients with AD, iNPH patients have a relatively mild memory impairment and a rather severe impairment of attention, calculation, executive function and psychomotor speed, possibly reflecting less medial temporal lobe impingement and more accentuated frontal lobe or fronto-subcortical changes (128).

Recently, Katzen et al. (131) compared iNPH patients (n=12) to age- and education-matched HI (n=9). All subjects were tested at four occasions (preoperatively and 2 weeks, 3 months, and 6 months after surgery), in order to detect treatment effects in iNPH not attributable to practice effects. Among the included neuropsychological tests (the MMSE, Boston naming test, Digit span, Symbol digit, Phonemic and Semantic fluency, the revised Hopkins Verbal Learning test (HVLT-R, learning and delayed recall), Trailmaking (versions A and B), Line tracing time, Serial dotting time, Finger tapping (dominant hand), and the Grooved pegboard (dominant hand)) the only one to show a significant time by group interaction effect after six months of treatment was the Trailmaking B.

There was only a marginal change on the MMSE (from mean values of 24.5 to 25.8, (cf. the previously mentioned study by Iddon et al. (109), but also study II). On the other hand, there was a number of speeded psychomotor tests where the differences between the preoperative and the 6 months assessments appeared to be substantially larger among the iNPH patients than in the control group (Symbol digit, Trailmaking A, Finger tapping and Grooved pegboard), and with somewhat larger samples they may well have turned out statistically significant.

Solana et al. (132) had interests that were related to those of Katzen et al., (131) but approached the problem of retest effects from a different angle. They tested untreated iNPH patients (n=32) and healthy volunteers (n=30) on four consecutive days with a battery of tests that comprised the Bingley memory test, the Tolouse-Pieron test, Trailmaking test A, Grooved pegboard, and a phonemic verbal fluency test. The authors found a significant learning effect among the patients on the Tolouse-Pieron test, but not on the other tests, whereas the healthy volunteers gained significantly from practice on the Tolouse-Pieron, Grooved pegboard and Trailmaking test A.

The matter of practice effects remains unresolved. Direct comparisons between changes in HI and changes in iNPH patients following treatment will probably conceal some of the actual effects of treatment, since learning is not independent of initial performance (133). Conversely, even if the assumption of an absence of learning effects in iNPH may hold for some tests and/or at lower levels of baseline performance, it may be seriously misleading for other tests and/or higher initial performance levels. The two latter studies (131, 132) point to the necessity to adopt new methods in the evaluation of neuropsychological effects of shunt treatment.

1.7. Scales for the assessment of INPH severity and treatment outcome

There is no standard for the grading of severity of iNPH, nor for the assessment of treatment effects. Different scales have been developed and continue to be developed, typically appearing in one or a few publications before being revised or abandoned. When scales are used repeatedly, they are rarely presented at length and at times the original articles are hard to come by. Hence, in this section some of the more frequently used scales have been gathered for the sake of accessibility.

Stein & Langfitt Scale, 1974 (134)

Grade 0 = No neurological deficit, able to work
Grade 1 = Minimal deficit, able to function independently at home
Grade 2 = Some supervision required at home
Grade 3 = Custodial care required despite considerable independent function
Grade 4 = No practical capacity for independent function

Rankin scale, 1957 (135)

0 = No symptoms at all
1 = No significant disability despite symptoms; able to carry out all usual duties and activities
2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3 = Moderate disability; requiring some help, but able to walk without assistance
4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6 = Dead

The scale was later modified by Boon et al. (136) (and referred to as the modified Rankin scale) who added a new step placed between the original scores of 3 and 4:
ñ4 = Moderate disability; partially independent, needing assistance <50% of the dayò (136).

Black Scale, 1980 (137)

Excellent	=	Resumed pre-illness activity without deficit
Good	=	Resumed pre-illness activity with deficit, improved in two or more categories
Fair	=	Improved but did not return to previous work, improved in one category
Transient	=	Temporary major improvement
Poor	=	No change or worsening
Dead	=	Died within 6 weeks of surgery or as a result of surgery

Kiefer Scale, 1994 (138)

Mental state

0=No clinical detraction
1=Concentr. disorders, forgetfulness
3=Apathy, partly oriented and symptoms of grade 1
5=Completely. disoriented, skill disorders

Gait disorders (GD)

0=No GD
0=GD only detectable in special tests (eyes closed)
2= Atactic and wide based, but secure (without help)
4= Walking is difficult and only with help possible
5=Only a few steps with help of other persons
6=Impossible to walk

Incontinence

0=No incontinence
3=Temporary incontinence (e.g., at night)
4=Permanent incontinence
6=Incontinence of urine and stool

Vertigo

0=No vertigo
1=Vertigo only under stress
3=Intermittent vertigo
4=Permanent vertigo

Headache

0=No headache
1=Intermittent (e.g., at night) or permanent headache
4=Heavy, permanent headache

Kiefer Scale score (KSS) =sum of scores across symptoms (0-25)
Recovery rate= (Preoperative KSS-Postoperative KSS) x 10/Preoperative KSS (max 10)

Kiefer Index, 2002 (139)

Mental state

0=No apparent deficit
1=Forgetful, impaired concentration
4=Apathy, or only partly oriented
6=Totally disoriented

Gait disorders

0=Not or only in special tests handicapped
2=Wide legged but per se safe gait
4=Troublesome gait, only with crutches possible
5=Only a few steps with the aid of one person possible
6=Unable to walk

Incontinence

0=None
1=Urge-incontinence
3=Intermittent bladder incontinence
4=Permanent bladder incontinence
6=Bladder and bowel incontinence

Dizziness

0=None
1=Intermittent spontaneous dizziness
2=Permanent dizziness

Headache **Kiefer index**, 2002 (139) continued

0=None
1=Intermittent (any severity) or permanent moderate headache
4=Permanent severe headache

Kiefer index (KI)=sum of scores across symptoms (0-24)
Recovery index = (Preoperative KI ï postoperative KI) x 10/Preoperative KI (max = 10)

Krauss Scale, 1996 (140)

Gait
0=normal,
1=cautious gait or impaired tandem gait
2=considerably unstable gait
3=unaided gait not possible

Incontinence
0=normal
1=sporadic incontinence or urge phenomena
2=frequent incontinence
3=no or only minimal control of bladder funct.

Cognitive impairment
0=normal
1=minimal attentional or memory deficits
2=considerable attentional or memory deficits but oriented to situational context
3= not or only marginally oriented to situational context

Improvement grades for each symptom:
0=no or only poor improvement
1=fair or good improvement
2=excellent improvement

Total improvement index (0-1): summed improvement grades/maximal improvement grades

Grading scale for NPH, established by the Research Committee on Intractable Hydrocephalus, the Ministry of Health and Welfare of Japan, 1996 (141)

Gait disturbance
0 = normal
1 = unstable, but independent gait
2 = walking with one cane
3 = walking with 2 canes or a walker frame
4 = walking not possible

Dementia
0 = within normal range
1 = no apparent dementia but apathetic
2= socially dependent but independent at home
3 = partially dependent at home
4 = totally dependent

Urinary incontinence
0 = absent
1 = absent but with pollakiuria or urinary urgency
2 = sometimes only at night
3 = sometimes even during the day
4 = frequent

Score on the Grading Scale for NPH = sum of scores across symptoms (0-12)
Improvement: ≥1point change

Dutch NPH Scale, 1997 (142)

Gait scale = WS+ SS+TS (2-40)

Walking score (WS)		Number of steps (SS) and time (TS) needed to walk 10 ms, mean of three attempts:			
Able to walk independently		Steps	Score (SS)	Seconds	Score (TS)
Tandem walking disturbed	2	<13	1	<10	1
Turning disturbed	2	13-15	2	10-11	2
Trunk balance disturbed, sway	2	16-18	3	12-13	3
Wide based stride	2	19-21	4	14-15	4
Small steps	2	22-25	5	16-18	5
Reduced foot-floor clearance	2	26-29	6	19-21	6
Start hesitation	2	30-33	7	22-24	7
Tendency toward falling	2	34-38	8	25-27	8
Total	WS=0-16	39-43	9	28-30	9
Able to walk with assistance	WS=18	>43	10	>30	10
Not able to walk at all	WS=20				

Dementia scale=WT+DS+TM+FT (4-40)

Ten word test (WT) recall after 5 min.	Digit span (DS) Forward+backward	Trailmaking A (TM) seconds	Fingertapping (FT) 10 sec, average of 3 attempts

Score	1	2	3	4	5	6	7	8	9	10
WT	>8	8	7	6	5	4	3	2	1	0
DS	>11	11	10	9	8	7	6	5	4	3
TM	<45	<61	<76	<91	<106	<121	<151	<181	<211	>210
FT	>45	>40	>36	>32	>28	>24	>20	>16	>12	<13

NPH scale = Gait scale + Dementia scale (6-80)

NPH scale, Owler et al. 2004 (81), modified from Larsson, 1991 (not shown) (143)

Gait	**Living conditions**	**Urinary symptoms**
0 = normal	0 = independent	0 = none
1 = insecure	1 = at home with assistance	1 = present
2 = insecure (cane)	2 = retirement home	
3 = bimanual support	3 = nursing home	
4 = aided	4 = hospital	
5 = wheelchair		

NPH scale score = sum of scores across domains (0-10)

NPH Grading Scale, Eide 2006 (144)

Gait disturbance

5=Normal gait

4=Gait is abnormal, but possible without support. Imbalance at turns with short steps.

3=A cane is needed. Independent walking is possible but is unstable or the patient falls.

2=Support from another person is needed. Ambulation is possible with help.

1=Patient is bedridden or not able to ambulate.

Urinary incontinence

5=No subjective or objective incontinence.

4=Urinary urgency. Rare incontinence.

3=Occasional urinary incontinence.

2=Continuous urinary incontinence.

1=Both urinary and faecal incontinence.

Dementia

5 = Normal.

4 = Memory problems exist that are reported by patient or family.

3 = Important memory problems with more or less severe behavior disturbances.

2 = Severe dementia.

1 = Vegetative.

NPH Grading Scale score = sum of scores across symptoms (3-15)

Improvement categories: ≥5 very significant improvement, 3-4 significant improvement, 1-2 slight improvement, -4-0 non-responders

iNPH Grading Scale (iNPHGS), Kubo 2007 (145)

Cognitive impairment

0 = normal

1 = complaints of amnesia or inattention but no objective memory and attentional impairm.

2 = existence of amnesia or inattention but no disorientation of time and place

3 = existence of disorientation of time and place but conversation is possible

4 = disorientation for the situation or meaningful conversation impossible

Gait disturbance

0 = normal

1 = complaints of dizziness of drift and dysbasia but no objective gait disturbance

2 = unstable but independent gait

3 = walking with any support

4 = walking not possible

Urinary disturbance

0 = normal

1 = pollakiuria or urinary urgency

2 = occasional urinary incontinence (1ï 3 or more times per week but less than once per day)

3 = continuous urinary incontinence (1 or more times per day)

4 = bladder function is almost or completely deficient

No total score, the subscales are kept separate; Dementia (0-4), Gait (0-4), Urinary (0-4)

Improvement: ≥ 1point change in one domain

The use of different tools to grade severity and different ways to define change, often makes it hard, at times impossible, to compare studies, both with regard to the samples included (beyond simple demography) and the results (cf. section 5.3.). There is a great need for an agreement on how to quantitatively express the severity of the iNPH symptomatology and the magnitude of change following interventions (i.e. shunt treatment, but also rehabilition programs or cognitive training etc.).

The demands that could reasonably be placed on a common scale would be that it should, at least, include assessments of all of the most salient symptoms of iNPH. Further, the level of measurement should be the highest possible (interval rather than ordinal when possible). This is especially important in the realm of neuropsychology, since it is well known that even (brain-)healthy individuals are poor at estimating their own neuropsychologal strengths and weaknesses (cf. (146)). As yet, there is a deplorable lack of neuropsychologists in the field of iNPH treatment and research.

Another wished-for feature of an iNPH scale would be that it should quantify severity in a way that is based on normality, at one end, and on the most advanced symptomatological stage, at the other, so that the numerical expression representing a patient should, instantaneously, provide the experienced clinician with an intuituve impression of the condition.

2. AIMS of the study

I To describe the neuropsychological performance of prospectively included patients with iNPH in comparison to similarly aged HI, and to examine its relation to neurological signs, vascular comorbidity, and background factors.

II To evaluate the effects of shunting on neuropsychological performance in INPH patients, and to estimate the predictive value of tentatively important factors.

III To assess a small selection of neuropsychological tests in terms of expediency, discriminability, and ability to depict changes following shunt treatment, in the context of the prospective European multicentre study on iNPH.

IV To present the outcome after shunt surgery of 142 iNPH patients included in the Eu-iNPH study using the newly developed iNPH scale and the modified Rankin scale as outcome measures.

3. PATIENTS AND METHODS

3.1. Patients

The 64 iNPH patients originally included in study I were consecutive cases referred to and preoperatively examined at the hydrocephalus unit, Sahlgrenska university hospital, during a period of seven years (1st of January 1999 - 31st of December 2005). In order to make comparisons with the sample of HI fair with regard to the influence of age, six patients below the age of 50 years were excluded from the analyses.

In study II, consecutive cases referred to and examined both pre- and postoperatively (3 months after surgery) during a period of eight years (1st of January1999 - 31st of December 2006) were included. Out of 56 treated patients, nine were excluded due to incomplete reexaminations, leaving 47 patients in the study. The age restriction applied in study I was dropped in study II, since the most important comparisons in that particular study were those between pre- and postoperative results. The majority of the patients in study II had also been included in study I.

The catchment area, Västra Götalandsregionen, had ~1.6 million habitants during these periods. With an estimated incidence of iNPH of 1/100 000/year (based on the two previously mentioned Scandinavian studies (88, 147)), at least 112 patients could possibly have been eligible to participate in study I, and 128 in study II.

In studies III and IV, 142 cases were examined before surgery (n=142), after three months (n=123), and after one year (n=115) of treatment. Again, these were consecutive patients, but included at 13 different centres in Europe, participating in a multicentre study aimed to investigate the prognostic value of the CSF tap test and R_{out}. In order to calibrate the iNPH scale developed in study IV, data from 100 consecutive iNPH patients examined at the Hydrocephalus unit were used.

The diagnostic criteria used in the different studies are presented below.

Table 6. Diagnostic critera in the studies I-IV.

Studies I and II iNPH	Studies III and IV Typical iNPH	Studies III and IV Questionable iNPH
History and clinical findings		
Insidious onset and lack of antecedent causes of sNPH Typical gait disturbance (mandatory) combined with (either or both) organic mental symptoms and urinary incontinence.	Gradually developed gait disturbance of both legs affecting tandem walking, turning, stride length and base. Mild to moderate cognitive impairment with onset together with gait disturbance or later.	Less typical gait disturbances. None, more severe (MMSE <21) or atypical (aphasia, apraxia, agnosia) cognitive symptoms.

Table 6 continued. Diagnostic criteria in the studies I-IV.

Imaging		
EI >0.30 according to CT or MRI Open aqueduct	EI ≥0.30 Symmetrical quadriventricular enlargement without obstructions. Absence of other clinically relevant parenchymal lesions.	EI ≥0.30 Symmetrical quadriventricular enlargement without obstructions. (Single cortical infarcts, moderate cortical atrophy and moderate to severe leukoaraiosis accepted.)
Physiological data		
Lumbar CSF pressure < 18mmHg (~24.5 cmH_2O)	Lumbar CSF pressure ≤ 18mmHg (~24.5 cmH_2O)	Lumbar CSF pressure ≤ 18mmHg (~24.5 cmH_2O)

3.2. Healthy individuals

One hundred and eight HI from senior associations and church communities who voluntarily underwent neuropsychological testing were included in study I. Individuals with neurological disorders or serious psychiatric disorders were excluded. Stable medical conditions and minor psychiatric disorders, however, were accepted. This group of HI also participated in another study with a restricted age range (≥ 50 years), which set a lower limit for the age distribution in study I.

When it was time to analyze the data for study II, another 51 volunteers had been added to the sample, which now consisted of 159 individuals.

One hundred and eight HI were included in study III. These were collected from the previous sample of 159 individuals, but the lastly included female participants were excluded in order to make the sex distributions more similar between groups.

In study IV data from 48 HI aged 68-73 (the manuscript states 70-74, which is incorrect) were used to establish normal values for an age range that may be considered most typical for iNPH patients. These 48 HI constitutes a subsample of the 159 included in study II.

3.3. Clinical examinations

The patients included in study I and II were neurologically and physiotherapeutically examined according to the standard procedure of the Hydrocephalus unit (100, 143). The examinations included ratings of gait, balance, and continence, as well as quantifications of global intellectual performance (by means of the mini-mental state examination, MMSE (105)), gait speed and stride length. An MRI investigation, including CSF flow sensitive sequences was also included in the routine. The complete procedure was repeated at follow-up, i.e. three months after surgery (study II).

The patients included in studies III and IV were investigated according to a protocol with the same constituents as the protocol for studies I and II, but they were also subjected to a CSF tap test and a CSF dynamic test for the assessment of R_{out} and compliance.

3.4. The neuropsychological examination

The initial clinical interview is aimed to capture the history of the patient from a social, educational and occupational perspective. The patient is also asked to describe his/her symptoms, their onset and progression. The interview provides the context that is necessary to identify the organic psychiatric manifestations of the condition, and also serves the purpose of getting the patient acquainted with the situation and the clinician. After the interview, a series a neuropsychological tests were administered:

Simple Reaction Time (study II). This is a computerised task, developed at our unit. The subject is instructed to fixate a white cross placed in the middle of a black screen on a laptop computer and to press the space bar as fast as possible when the screen turns white. Twenty stimuli are preceded by six practice stimuli. The fixation intervals vary randomly between 2 and 6 seconds. The variable that was used was the mean reaction time of subjects.

Target Reaction Time (studies I and II). This is a computerised go no-go task, developed at our unit. The subject is instructed to fixate a white cross on a black screen (the same as in the Simple Reaction Time task) and to press the space bar as quickly as possible when the screen turns white (go condition), but to avoid pressing it if the screen turns red (no-go condition). Go and no-go stimuli (20 of each kind) are presented in a pseudorandom order (with a maximum of three identical stimuli in a row) and preceded by six practice stimuli. Again, the length of the fixation intervals varies randomly between 2 and 6 seconds. The variable that was used was the mean reaction time of the subject in the go condition.

*Tracks (studies I and II).*This task was constructed by Baddeley et al. (148) as the motor half of a dual task. The subject is provided with a paper with 80 squares connected by straight lines, and instructed to cross the boxes with a pencil as quickly as possible in the order indicated by the connecting lines during 60 seconds. The variables used were seconds per cross (study I) and the number of crossed squares (study II).

The digit span (studies I and II). This subtest of the WAIS-R (Pearson Education, Upper Saddle River, New Jersey) consists of series of digits. The subject is instructed to repeat the digits in each series as soon as it has been read aloud by the examiner. At first series are to be repeated in the same order as when presented. During the second part of the test the digits are to be repeated in the reverse order. The variables that were used were the maximum number of digits repeated forwards (studies I and II), the number of digits repeated backwards (studies I and II), and a summary representing the number of correctly repeated series (the WAIS-R score)(study II).

The Grooved Pegboard (Lafayette Instrument Co., Lafayette, IN)*(studies I-IV).* In this widely used test of manual dexterity the subject is instructed to fit 25 pegs into holes with randomly positioned slots as quickly as possible. The first trial is performed with the dominant hand (row by row from left to right for right-handed subjects, from right to left for left-handed subjects), and the second with the nondominant hand (reversing the right-left order). The variables that were used were time in seconds to complete the trials with each hand (studies I-III), the sum of the two trials (studies I-III) and the time in seconds for the fastest trial (study IV).

The Auditory Verbal Learning Test(RAVLT)(122)*(studies I-IV).* The RAVLT, another widely used test, is designed to measure verbal learning and memory. The subject is instructed to recall and reproduce as many as possible out of fifteen concrete nouns read aloud on five consecutive trials. The five learning trials are followed by one trial with a

second list, whereafter the subject is asked to recall the words from the original list again. After a delay of 20-30 minutes the subject is asked to repeat the words from the original list. The variables that were used were the number of words recalled on the fifth trial (study I), the difference between the first and fifth trials (study I), the sum of words recalled across the five learning trials (studies I-IV), and the number of words repeated on the delayed recall trial (studies I-III).

The Swedish Stroop Test (149)*(studies I-IV).* This test consists of two tasks. In the first (colour naming) the subject is instructed to name the colours (blue, red, yellow, and green) of 100 rectangles as fast as possible. The second (the interference task) requires the subject to name the colour of the ink of 100 written colour words that are printed in incongruent colours (e.g., the word red printed in green). The variables that were used were the time in seconds to complete the first task (studies I-IV), the time in seconds to complete the interference task (studies I-IV), the percentual increment from the first to the second task (study I), and the difference in seconds between the two tasks (study II).

3.5. Statistical methods

Mostly, nonparametric statistics were used. Thus, the Spearman rank correlation coefficient (ρ) was used to estimate associations between variables, the Mann-Whitney U test and the χ^2 test (or Fishers exact test) were used to compare independent groups with regard to ordinal (or continuous) data and proportions, and the Wilcoxon signed-rank test was used for comparisons between repeated measurements. In study I a binary logistic regression analysis was performed to investigate and control for the influence of covariates on differences between groups. In study II the Bonferroni-Holm step-down method was applied to adjust alpha-levels for multiple comparisons. The area under the receiver-operating characteristic curve (ROC-AUC) was calculated in studies II and III to determine the discriminative efficiency of the neuropsychological tests. In studies II and III parametric methods were used to evalute changes ($\geq$ 1 sd), adhering to methods used in previous studies in the field (cf. section 1.6.4.3.) A customary, parametric limit for impairment ($\leq$ 1.5 sd below normative mean) was also used. All analyses were performed with SPSS for Windows (versions 13-17; SPSS, Inc., Chicago, IL).

4. RESULTS

4.1. Study I

The primary aim of the first was to compare the performance of iNPH patients to that of HI on a selection of neuropsychological tests, chosen on the basis of clinical experience, functional anatomic considerations and earlier reports in the literature. Another aim was to investigate the relationship between neuropsychological performance, on the one hand, and neurological signs, vascular comorbidity and background variables, on the other.

The iNPH patients performed significantly worse than the group of HI on all of the administered tests (also after controlling for length of education, which differed between the groups in the favour of HI), and practically all of the assessed variables proved to be good at discriminating between patients and HI (the majority of ROC-AUCs assuming values somewhere between 0.80 and 0.90).

The neuropsychological test results were correlated with the ratings of gait, balance, incontinence and hours of daily sleep. Furthermore, the correlations between seemingly independent neuropsyhological functions were strong in the group of patients and substantially weaker or absent among HI.

The analyses also revealed that the presence of risk factors for cerebrovascular disease added significantly to the severity of impairment on most tests, as did age.

4.2. Study II

The aims of study II were to investigate the effects of shunt treatment on neuropsychological performance and to estimate the influence on these effects of putatively important factors. Thus, the same tests as in the first study were used again, after three months of shunt treatment.

Statistically significant effects of treatment were seen on almost all of the assessed variables (the only exceptions from this rule were digit span forward and simple reaction time). The largest proportions of improved performances were seen in the Stroop tasks (82-91%) and on the Grooved pegboard variables (86-90%). With a definition of improvement that required a positive change of at least 1 sd (from the distributions of HI), most of the patients were found to be improved on several of the tests (82% improved on $\geq$ 4 out of nine variables).

The strength of the correlations between normally independent neuropsychological functions was reduced following treatment. However, the correlations were still substantially stronger than among HI.

The neuropsychological functions were improved but not restored; following three months of shunt treatment iNPH patients were still outperformed by HI.

4.3. Study III

In study III we aimed to evaluate the efficacy of the three neuropsychological tests that were used in the European multicentre study on iNPH (Eu-iNPH)(the Grooved pegboard, the RAVLT and the Swedish Stroop Test). This was also an opportunity to explore the reproducibility of our previous findings, hence a Swedish sample of HI (almost identical to the sample used in study I) was used for comparisons.

The efficacy of the tests and the eight variables derived from them was evaluated in terms of expediency (i.e., the suitability for administration in the group of patients, and

the expenditure of time), sensitivity and specificity (ROC-AUC values), and ability to detect changes.

RAVLT was found to be the most easily administered and accomplished task (completed by more than 90% of the patients), whereas the Stroop interference was the most often omitted or discontinued task (completed by ~70%). The total time for administration of the three tests was approximately 20 minutes.

The discriminative capacities of the tests were similar, with ROC-AUC values ranging from 0.86 (good) for RAVLT delayed recall to 0.95 (excellent) for Grooved pegboard (sum of both hands).

All of the variables were significantly improved following treatment, but unchanged between the two follow-up examinations (3 and 12 months after surgery). The proportions of patients who improved more than one standard deviation varied from 16% (RAVLT) to 59% (Grooved pegboard).

Corroborating the earlier findings in smaller samples of Swedish patients, the European patients were outperformed by HI (and the presence of risk factors for cerebrovascular disease made the deficits more severe), and performance on the selected tests was significantly improved following treatment, yet not reaching the levels of performance of HI.

4.4. Study IV

The explicit objective of study IV was to present the outcome after one year of shunt treatment in the Eu-iNPH study, using a new iNPH scale and the well known modified Rankin scale. In fact, the lions share of the work was devoted to the construction of the new scale, and an implicit aim was therefore to evaluate the behavior of the scale itself.

The improvement rate among those who completed the study was 83% according to the iNPH scale and 69% according to the modified Rankin scale.

Preoperatively, 81.6% of the patients displayed symptoms in all of the domains covered by the iNPH scale (gait, balance, neuropsychology and continence), whereas 17.7 had a normal function in one of the domains, making a sum of 99.3% and pointing to a considerably more cohesive syndrome than is generally thought.

The iNPH scale was intented to cover the whole range of severity and to capture even the small changes hoped for in patients who experience only mild symptoms before treatment. These goals were accomplished.

5. DISCUSSION

The primary objective of this thesis was to identify and describe the neuropsychological deterioration associated with idiopathic normal pressure hydrocephalus and, as a mean to that end, to select tests that are appropriate for routine clinical assessment of iNPH. Other major aims have been to describe neuropsychological changes following treatment, to investigate the impact of cerebrovascular comorbidity, and to develop an iNPH scale that, hopefully, could gain widespread approval.

5.1. Tests, selection and findings

Previous studies have, with a few exceptions, described the preoperative deficits and postoperative changes in mixed samples, i.e., including both idiopathic and secondary cases. Conducting neuropsychological examinations with patients with sNPH, and not the least, observing their sometimes dramatic improvement following shunt surgery, belongs to the most rewarding and encouraging tasks in clinical neuropsychology. The neuropsychological deficits and the organic psychiatric syndromes of iNPH are less severe at baseline, and the specific impairments that are caused by another primary pathogenic event and aggravated by the subsequent and often rapid development of hydrocephalus in sNPH, are lacking. Similarly, although the improvement of iNPH patients following surgery is both important and gratifying, it generally falls short of overwhelming. Thus, with clinical experience it was realized that, from a neuropsychological viewpoint, secondary and idiopathic cases of NPH should be studied separately.

The selection of neuropsychological methods was based on clinical experience with NPH patients (i.e., a mixed experience), available literature, and functional anatomic hypotheses. Thus, the measurement of reaction time was motivated by the observation of impaired wakefulness and slowness of many of our patients, along with their own reports of increased daytime sleep and a propensity to fall asleep.

Hypothetically, this could be linked to pathological changes involving the ascending arousal system at any level, however most likely at the level of thalamus and hypothalamus due to the dilation of the third ventricle, and/or at higher levels, due to impingement on thalamocortical circuitry. Similar reasoning supported the development and administration of the target reaction time task (go no-go), yet with the additional requirements of reflection and response inhibition. The time needed to reflect and decide whether to respond or not, was prolonged in patients with iNPH (cf. studies I and II) and it was significantly shortened following treatment. Simple reaction time (the go condition), however, was normal at baseline and unchanged at follow up. Analyses of data from our own unit show that this is not the case in sNPH, where simple reaction time is significantly prolonged at baseline and responds well to treatment, a finding that is similar to those presented by Thomsen et al. (150) in a mixed sample with a majority of sNPH patients. This dissociation between simple reaction time and the time to respond after reflection and decision making, may be linked to findings in recent experimental studies by Forstmann et al., (151, 152) pointing to an important role of the pre-supplementary motor area (pre-SMA)-striatal circuitry in healthy individuals handling simultaneous demands of speed and accuracy.

The assessment of dexterity by means of the Grooved pegboard (the Tracks task served the same purpose, but will not be discussed here since it was not used throughout the studies of this thesis), was based on the frequent observations at the Hydrocephalus unit of motor deficits beyond the well characterised problems with gait (cf. (100)). The marked difficulties faced by iNPH patients when performing this task, as evidenced in general quantitative terms (time for completion) in studies I-III, have several qualitative features that would lend themselves to more systematic studies. More specifically, whereas the main obstacle for some patients appears to be slow (but smooth) movements, a larger proportion display problems pertaining to deficient regulation of muscle tone, repeatedly appearing to force the pegs into place. Others, again, appear to achieve similarly poor quantitative results, mostly or partly, due to spatial difficulties, as indicated by a marked tendency to tilt the pegs instead of bringing them into place perpendicularly to the surface of the board, by misjudging the horizontal rotation of the pegs (often by 180 degrees), or by simply being poor at aiming. The Grooved pegboard works well for clinical routine purposes, whereas attempts to disentangle the various components that contribute to the overall subnormal performance would require the administration of a series of more specific subtasks in a more experiment-like situation.

Disturbances of anterograde declarative memory, i.e., a reduced ability to recall recent personal experiences and to acquire new information, are the most frequently reported cognitive problems among those that are spontaneously reported or affirmed by patients with iNPH and their relatives. Such memory and learning deficits are generally referred to as episodic memory difficulties, and even though the concept of episodic memory actually encompasses several features that are not normally assessed - or even considered - in the clinical situation (153) the concept will be used here as well. Thus, dysfunction of the episodic memory system, as it is operationally defined here, is evidenced through an impaired ability to learn new information, and to retrieve recently learned information.

Episodic memory is associated with structures and pathways within the circuit of Papez-MacLean (154). This circuit consists of three major fibre bundles and more sparse connections between the thalamus and the cingulate gyrus. One of the bundles connects the hippocampus with the mammillary bodies through the fornix, whereas a second connects the corpora mammillaria to the anterior thalamic nucleus through the mammillothalamic tract. The third connects the subiculum with the cingulate gyrus through the cingulum (155). Impingement on these pathways (especially the former two) is associated with disorders of episodic memory, e.g., Aggleton et al have shown that damage to the fornix (due to colloid cysts in the 3rd ventricle or their surgical removal) is quite sufficient to cause impaired learning and recall (156). The frontal lobes have also been shown to be important for episodic memory, however, their role appears to be more associated with encoding and retrieval, than with storage itself. Budson & Price (157) present an ñoversimplified but clinically usefulò analogy to describe the frontal and the medial temporal (including the Papez-MacLean circuit) contributions to episodic memory by describing the frontal lobes as a ñfile clerkò and the temporal lobes as the ñrecent memory file cabinetò (remote memories are considered to be stored in other cortical regions, in a ñremote file cabinetò).

The patientsô complaints and the close proximity to the ventricular system of the tracts and structures within the Papez-MacLean circuit, make memory assessment mandatory in the neuropsychological evaluation of patients with iNPH. Not surprisingly, we found our patients to perform worse than HI on the RAVLT variables, and to be significantly

improved following surgery. However, the same line of reasoning as the one concerning the Grooved pegboard may be applied here; the administration of more specific subtasks (or analyses of already available variables), may enable us to estimate the contributions of different components to the final overall result.

Attention, speed (psychomotor or information processing) and executive functions are often mentioned in connection with iNPH (e.g., (109, 119, 126, 128, 158-160). Patients may describe or admit that they experience concentration difficulties, that their thinking appears slower than before the onset of iNPH symptoms, and that they have problems with the planning, initiation and purposeful execution of actions (mostly, though, in terms of reduced motivational capacity and lack of interest). The Stroop test, as administered here (studies I-IV) gives the opportunity to measure speed in the performance of a very simple task, with a minimal motor requirement (colour naming), and the ability to maintain attentional and cognitive control in the face of interference. Attention, and - even more so - executive function, are broad concepts, subsuming ranges of functions, some of which may be more or less independent of one another. Hence, in the studies of this thesis, we have preferred to avoid them.

The structures most consistently shown to be involved in the Stroop interference task are the anterior cingulate and the dorsolateral prefrontal cortex (161, 162). However, the head of the left caudate has been shown to be involved specifically in word interference (163), and, further, performance on the task has been shown to be related to age related white matter changes and the presence of vascular risk factors (diabetes and hypertension, independent of the severity of the measurable white matter changes)(164) and reductions of the area of the corpus callosum (165).

The two subtasks of the Stroop test, both revealed marked deficits in patients with iNPH at baseline (studies I-IV) and significant changes following treatment. In fact, in some patients interference is evident already in the simple condition (i.e., naming the colours of rectangles), when the responses are, as it seems, triggered by the colours of adjacent rectangles instead of the intended one.

Through the years of work with this thesis, the Grooved pegboard, the RAVLT, and the Swedish Stroop test have established themselves as a core battery in the investigations of iNPH patients at our unit. These tasks capture the essentials of the neuropsychological effects of the disorder. Which tests should be used in order to separate iNPH from other disorders, and to predict outcome, remains to be investigated. Similarly, as mentioned earlier, the relationship between OPDs and neuropsychological performance awaits future studies.

5.2. Evaluation of the tests

There are several methods, but no common standard for the evaluation of the appropriateness or efficiency of neuropsychological (or other) tests. In studies I and III, the abilities of the selected tests to discriminate between patients with iNPH and HI were investigated by means of ROC-AUC-values. Neuropsychological tests or variables that failed did not readily distinguish between iNPH and HI were deleted (e.g., the Digit span and the percent increment on the Stroop test). Admittedly, there are more commonly used metrics to quantify and present the diagnostic utility of tests (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios). It may prove worthwhile to compare tests with regard to sensitivity and specificity, if the purpose

were to select the most diagnostically useful tests. Nevertheless, applying the other metrics to that end would be less meaningful, mainly due to the rarity of the disorder.

In study III, the tests were evaluated also in terms of their expediency (usability and time for administration), and their ability to detect changes following treatment.
In the hands of trained neuropsychologists, all of the three tests included in studies III and IV are expected to be administered at virtually all times (situations where iNPH patients refuse to cooperate are extremely rare). Thus, missing values are, in general, to be interpreted as evidence of severe functional impairment (cf. study IV).

The evaluation of change following treatment is a more complicated and, as yet, unsettled issue. In the section titled Neuropsychological impairment and change (p. 21), some previously used ways of defining and assessing neuropsychological change in iNPH were presented, some of which were used, along with new approaches, in studies II and III. All of these methods, however, are used in want of a more adequate approach. For future purposes, we have recently collected data from a sample of Swedish HI (n=104), using a test-retest interval of three months (corresponding to the customary interval between surgery an follow up at our unit). This procedure replication will enable us to use reliable change indices (see Maassen et al. (166) for a comparison between different indices), to determine whether and by how much a specific quantitative change exceeds what can be expected from practice and measurement error.

5.3. Standards and the iNPH scale

Standardization enables comparability and reproducibility. The establishment of common diagnostic criteria for iNPH has brought about a substantial improvement in this regard, as would standards for the definitions of other concepts and for the measurements of pertinent variables (be it in the field of neuropsychology, locomotion, CSF-dynamics, functional imaging, quality of life, or any other relevant area). Reviewing methods for outcome assessment, Klinge et al. (85) noted that ñthe scales used and the time at which patient outcome is measured are extremely variable throughout the literatureò (p 50). Hopefully, the iNPH scale introduced in study IV, will gain a broader acceptance than its predecessors. There are some reasons why it should. Firsty, it includes the four domains that are most commonly affected in iNPH, gait, neuropsychology, balance and continence. Most, but not all, existing scales rate the severity of mental, gait and continence problems, however, none of them acknowledge the frequent (and treatment amenable) balance disturbances per se. Secondly, measurements of continuous variables are used to establish the severity of neuropsychological impairment and to supplement the rating of the gait disturbances. A similar approach is seen in the Dutch scale (142), but with the inclusion of a neuropsychological test that is less capable of identifying iNPH related deficits and, consequently, less likely to identify improvement after surgery (the Digit span). Thirdly, since the disturbance of gait is generally considered the most important symptom by patients, relatives and clinicians, it has been given twice the weight of that of each of the other domains (cf. (167). Fourthly, the attainable scores range between 0 and 100, where 0 denotes the most severe symptomatology, whereas 100 represents absence of symptoms on ordinal ratings and normal performance on continuous measures. This is a concession to the Hindu-Arabic numeral system, intended to make the scores intuitively appealing. Fifthly, the conversion of continuous measures into subscale scores (for the gait and neuropsychology domains) was based on actual results of a sample of iNPH patients and on the results of HI. This implies that a score of 100 will be truly normal, whereas the

remaining scores will reflect the position of the individual in relation to other iNPH patients. Hence, severity ratings offer an empirically based meaning (eg., a score of 50 will, approximately, correspond to the 50^{th} centile of iNPH patients). Sixthly, there is a suggested limit for deciding whether a patient is improved or not ($\geq$ 5 point increment following surgery). Some previous scales also include definitions of change, whereas others do not.

Old habits die hard, and the willingness of other researchers to apply the new iNPH scale, will depend on future efforts at persuasion.

6. CONCLUSIONS AND REFLECTIONS

- iNPH is associated with neuropsychological deficits in most areas. Here, tests measuring dexterity, learning and memory, speed and swift regulation of mental and motor processes revealed substantial differences between iNPH patients and healthy individuals, differences that remained when patients with reductions of global intellectual level of functioning were excluded from the comparisons.

- The neuropsychological deficits in iNPH are strongly interconnected and related to other characteristics of the disorder, the disturbances of gait, balance and continence.

- iNPH might be pathophysiologically characterised as a suppression of overlapping circuitries adjacent to the ventricles; frontal corticoï basal gangliaï thalamoï cortical and limbic pathways, causing the interrelated and predominantly subcortical symptoms.

- A core battery consisting of the Grooved pegboard, the Rey Auditory Verbal Learning test, and the Swedish Stroop test is well suited to identify the neuropsychological impairment due to iNPH, and to detect changes following treatment.

- Risk factors for cerebrovascular disease aggravate the neuropsychological deficits of patients with iNPH and do so quite uniformly.

- The neuropsychological functions of iNPH patients improve significantly after shunt surgery, independently of the presence of vascular comorbidity, but only rarely return to normal levels.

- iNPH signs may be successfully evaluated, before and after shunt surgery, by a new iNPH scale introduced in this thesis, covering the domains of gait, neuropsychology, balance and continence by continuous and ordinal measurements.

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ORIGINAL ARTICLES I-IV