Thesis

Idiopathic normal pressure hydrocephalus in neurological practice

- A study of epidemiology and methods for selection of patients for surgery

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Til Gro

Abstract

Aims: The aims of this thesis are to estimate the epidemiology of iNPH in a Norwegian population compared to the incidence of surgery for the condition, to assess whether lumbar measurements of cerebrospinal fluid pressure (CSFP) concurs with intracranial pressure (ICP), and with the clinical response to shunting, and finally to assess which of the lumbar hydrodynamic measurements that best can predict the clinical response to shunting.

Methods: The thesis consists of six publications. Publication I assesses the prevalence of iNPH in a Norwegian population. Publication II assesses the five year incidence of surgery for iNPH in Norway. Publication III compares lumbar CSFP waves versus ICP waves in iNPH. Publication IV compares ICP measured simultaneously within the brain parenchyma and cerebral ventricles. Publication V assesses the role of lumbar infusion testing for referral of iNPH patients to neurosurgery. Publication VI assesses whether CSFP wave amplitude during lumbar infusion in iNPH can predict response to shunting.

Results: We found a prevalence of probable iNPH of 21.9/100.000 inhabitants, and an incidence of 5.5/100.000/year. The total rate of surgery for iNPH was 1.09/100.000/year. The lumbar CSFP wave amplitude during lumbar infusion could be used to predict the ICP wave amplitude during over-night monitoring of the intracranial pressure. There is no pressure gradient between pressure wave amplitudes derived from brain parenchyma and ventricular CSF. Resistance to outflow (R_{out}) and CSFP wave amplitude derived from lumbar infusion related only weakly, while shunt response related highly to the quantitative distribution of CSFP wave amplitudes during infusion, giving false negative results in 16% of the patients. Elevated CSFP wave amplitudes during lumbar infusion predicted shunt response with a sensitivity of 88 and a specificity of 60.

Conclusions: Our data suggest that too few patients are being offered surgical treatment for iNPH in Norway. Lumbar CSFP wave amplitudes concur to a great extent with ICP wave amplitudes and with clinical response to shunting. Lumbar CSFP wave amplitudes predict clinical response to shunting better than R_{out}, but further studies are advocated to address the problem of false negative results from lumbar hydrodynamic measurements.

Contents

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The project arose from a rather vague idea of trying to gain in-depth knowledge about a syndrome which in my first years as a resident fellow in neurology seemed confusing and little tangible, but in which I had witnessed that the surgical treatment sometimes could give astonishing effects. For this purpose, I approached Dr. Per Kristian Eide at the department of Neurosurgery, Oslo University Hospital. I am greatly indebted to him for taking on the responsibility of main supervisor. His tremendous and encouraging enthusiasm, support, creativity and constructive criticism have been the *sine qua non* for this work. Since I have conducted the main part of the project in the long after-hours of the daily clinical work, his endurance has been crucial, together with his always well-founded comments on every part of the progression of the work.

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Abbreviations

CSF: Cerebrospinal fluid.

CSFP: Cerebrospinal fluid pressure

CSFP-Q_{pulse}: Pulse wave amplitude of the CSFP.

CT: Computer tomography.

dP: Pulse pressure amplitude.

dT: Pulse pressure latency.

ELD: External lumbar drainage.

EVD: External ventricular drainage.

GCS: Glasgow coma score.

ICP: Intracranial pressure.

IE: Intracranial elastance.

iNPH: Idiopathic NPH.

LP-shunt: Lumboperitoneal shunt.

MCA: Middle cerebral artery.

MMSE: Mini mental state examination.

MRI: Magnetic resonance imaging.

NPH: Normal pressure hydrocephalus.

NPV: Negative predictive value.

PAR: (cerebral) parenchyma.

Po: Opening pressure.

Pp: Plateau pressure.

PPV: Positive predictive value.

R_{out}: Resistance to outflow.

SAH: Subarachnoid hemorrhage.

sNPH: Secondary NPH.

VA-shunt: Ventriculoatrial shunt.

VP-shunt: Ventriculoperitoneal shunt.

Publications included in thesis

This thesis is based on the following papers, which will be referred to in Roman numerals as listed below.

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

II. Brean A, Fredø HL, Sollid S, Müller T, Sundstrøm T, Eide PK: Five-year incidence of surgery for idiopathic normal pressure hydrocephalus in Norway. **Acta Neurol Scand** 120: 314-316, 2009.

III. Eide PK, Brean A: Lumbar cerebrospinal fluid pressure waves versus intracranial pressure waves in idiopathic normal pressure hydrocephalus. **Br J Neurosurg** 20: 407-414, 2006.

IV. Brean A, Eide PK, Stubhaug A: Comparison of intracranial pressure measured simultaneously within the brain parenchyma and cerebral ventricles. **J Clin Monit Comput** 20: 411-414, 2006.

V. Brean A, Eide PK: Assessment of idiopathic normal pressure patients in neurological practice: The role of lumbar infusion testing for referral of patients to neurosurgery. **Eur J Neurol** 15: 605-612, 2008.

VI. Eide PK, Brean A: Cerebrospinal fluid pulse pressure amplitude during lumbar infusion in idiopathic normal pressure hydrocephalus can predict response to shunting. **Cerebrospinal Fluid Research** 7(5): 1-11, 2010.

1. Introduction

1.1. Hydrocephalus - Historical overview

The concept of the cerebral ventricles as the domicile of the human intellect is probably the longest surviving theory of brain function, proposed by Herophilos (325 – 255 BC), and Erasistratos (304 – 250 BC) working in Alexandria in the 3rd century BC, and not definitely rejected until the end of the 18th century, thus surviving 20 centuries (1). According to the early theories, stemming from Alexandrian medicine and further elaborated by Galen (130 – 201 AD), the ventricles were not fluid-filled, but contained the "spiritus" or "pneuma"; a light gaseous substance considered the agent of the activities now attributed to the neurons of the brain parenchyma. The roots of this belief were to a great extent attributable to Aristotle (384 – 322 BC), who, in contrast to his predecessors Pythagoras (570 – 500 BC) and Hippocrate (approx. 460 – 370 BC), mistakenly attributed voluntary movement and intellectual abilities to the heart (2). The existence of the cerebrospinal fluid (CSF) was acknowledged by Andreas Vesalius (1514-1564) (3), but not universally recognized until Francois Magendie's (1783-1855) works in the early 19th century (4). In fact, even medical authoritative writers as late as Moritz Heinrich Romberg (1795-1873) thought that the ventricles were filled with "humid gas" (ibid).

Aulus Cornelius Celsus (approx 25 BC-25 AD) was the first to coin the term "hydrocephalus" in his work "On medicine": *"There is a class (of headaches) which may become chronic, in which a humour inflates the scalp, so that it swells up and yields to the pressure of the fingers. The Greeks call it hydrocephalus"* (5), probably meaning accumulation of fluid on the outside of the scull. However, it was not before 1768 that hydrocephalus was described as a distinctive clinical entity by Robert Whytt (1714-1766) (6).

Although Walter E. Dandy (1886-1946) described third ventriculostomy as early as in 1922 (7), an effective treatment for the condition was not developed until the 1930's, when the Norwegian neurosurgeon Arne Torkildsen (1899-1968) constructed his method of shunting CSF from the ventricular system to the cisterna magna (8). During the 1950's, the toolmaker John W. Holter (1916-2003), together with Eugene Spitz (1919-2006) at the Childrens

hospital in Philadelphia, developed the first working shunt valve for the treatment of hydrocephalus (9).

Assessment and monitoring of intracranial pressure (ICP) was introduced by Ernst Victor von Leyden (1832-1910) in 1866, performing fluid manometry in dogs (10). In 1878, Heinrich Quincke (1842-1922) introduced the spinal puncture technique (11). This technique quickly gained widely use in both diagnostics and therapy, even in Norway, as exemplified by to extensive reports in two Norwegian medical journals as early as in 1895 and 1897 (12; 13).

Measurement of ICP was introduced by Pierre Janny (1921-1993) in the 1950's (14), although Nils Lundberg's (1908-2002) later work was fundamental for the development of clinical useful ICP monitoring (15).

The coining of the term NPH can be dated to 1965, when Hakim, Adams and coworkers described a clinical triad of gait disturbance, mental deterioration and urinary incontinence coexisting with ventricular enlargement and a normal cerebrospinal fluid pressure on lumbar puncture (16; 17). However, several earlier papers described patients with progressive symptomatic hydrocephalus without overt signs of intracranial hypertension (18-25), in one instant even with relief of symptoms after shunting (25).

Some the first clinical series showed great surgical success (26; 27), but these were not confirmed by subsequent prospective studies (28-30), something which led to a decline in the rate of shunt insertions (31).

1.2. Clinical presentation

1.2.1. Motor symptoms

Gait disturbance is often the first clinical sign, and is also the most likely to improve after shunting (32-40). No "classical" NPH gait pattern is considered to exist, although several authors describe patients typically having a wide-based ataxic gait with frequent falls at an early stage, and at a later stage a small-stepped Parkinson gait with reduced foot floor

clearance and start hesitation (35;36;41;42). With progressing disease, turning often becomes difficult and requires several steps. This is often referred to as “en bloc”-turning (42). Detailed kinematic gait analyses have on the one hand confirmed the presence of specific gait abnormalities in NPH-patients, but have on the other hand shown that the gait in many aspects resembles the non-specific senile gait disorder with varying both pyramidal, extrapyramidal and cerebellar signs (34;43-46). Postural disturbances has also been described in NPH-patients, having a more forward leaning stance than healthy normal individuals, with a wider sway and an imbalance accentuated by eye closure (47;48). Hypokinesia, tremor and hypokinetic or hyperkinetic movement patterns have all been described in NPH-patients (49). The pattern of movement in iNPH-patients might resemble a parkinsonian pattern. In one study, parkinsonism, as defined by using the motor sections of the Unified Parkinson Disease Rating Scale (UPDRS), is reported as a symptom in 71% of iNPH-patients (50).

1.2.2. Urinary symptoms

Increased urinary urgency, and in later stages urinary incontinence, is a feature in NPH. Although the exact nature is not well characterized, there is evidence supporting the notion that these clinical features are directly caused by detrusor hyperactivity (51). Thus, in a recent study by Sakakibara et al, 95% of 41 patients with iNPH had urodynamic evidence of detrusor hyperactivity (ibid). Even though urodynamic studies show evidence of detrusor hyperactivity in most patients, urinary incontinence *per se* is therefore not always present, as shown in many clinical studies (42;52-54) The so called *incontinence sans gêne* might be present in later stages of the disease, probably due to frontal lobe dysfunction (35), while fecal incontinence might occur only in very late stages (42). Some authors argue that the incontinence also might not be a specific symptom in NPH, due to a considerable co-morbidity in the elderly, and that the late stage incontinence might be a secondary feature of gait disturbance and more global frontal indifference (55).

1.2.3. Cognitive symptoms

The most evident cognitive symptoms of iNPH, such as slowing of thought, inattentiveness, apathy and encoding and recall problems, point to a subcortical dementing process (54). Still, very many aspects of cognitive/mental functions might be affected in NPH, ranging from impaired wakefulness (56) to reduced attention and concentration (57), reduced psychomotor speed (58), reduced memory and learning (ibid) and reduced problem-solving, abstract reasoning and executive functions (59-62). In a study by Hellström et al, neuropsychological deficits were found over a broad range in 58 iNPH-patients as compared to healthy controls (63). This study confirmed earlier described associations between the severity of cognitive impairment and gait disturbances (64). The fact that the cognitive deficits are evident in multiple cognitive domains, and can be detected by a broad range of neuropsychological tests, is also reflected by an earlier study, showing that about 60% of iNPH-patients score less than 25 on the MMSE (65). Furthermore, it is not possible to differentiate between iNPH and Alzheimer's disease on the basis of subscores on the MMSE (64), nor has there been shown a specific neuropsychological profile that can reliably differentiate iNPH from other causes of cognitive decline (66).

1.2.4. Is NPH a clinical diagnosis?

As shown in sections 1.2.1 through 1.2.3, the different symptoms are not distinctive of NPH alone. Thus, NPH has no cardinal signs that can clinically distinguish the condition from other afflictions of the elderly. It has been proposed that the only reliable means of validating the diagnosis of iNPH is to demonstrate a favorable response to shunt treatment (26). However, this might result in a high incidence of both false negatives and false positives, as elaborated on in section 5.1.1. It is therefore clear that information from other modalities, as shown in section 1.6, is important in the diagnostic work-up.

1.3. Classification

Traditionally, NPH is divided in two distinct subgroups, depending on the presumed cause in the individual patient. This was evident already from the three NPH-cases described by Hakim and Adams in 1965 (17), where two cases were post-traumatic, and one was idiopathic. NPH without any known cause is still classified as *idiopathic NPH* (iNPH), while NPH preceded by a presumed causative pathological event is called *secondary NPH* (sNPH). The most important known causative events are head trauma, intracerebral or subarachnoidal hemorrhage, infection or brain tumor (36;37;67). The exact distribution of patients between the two diagnostic groups is not fully known. In a multicenter study from Amsterdam constituting a total of 152 patients, 127 (84%) was classified as having iNPH, and 25 (16%) was classified as having sNPH (68). In a later Dutch multicenter study constituting a total of 101 patients, 89% were classified as having iNPH, and 12% was classified a having sNPH (43). Nevertheless, some authors claim that the distribution between iNPH and sNPH is approximately 50/50 (39;53;69;70).

Several of the clinical studies in the field do not make a clear distinction between iNPH and sNPH when including, diagnosing, treating or evaluating the patients (31;43;66;71-74). As for iNPH, guidelines for the diagnosis and management have been proposed (75), excluding patients with sNPH. The authors of the guidelines state that this subdivision was made to help simplify the diagnostic approach because the potential for recovery in sNPH patients would be more influenced by co-morbidity, but that they learned, in the process of making the guidelines, that co-morbidity was equally important in an iNPH population (ibid). Thus, even though a distinct classification according to the presumed cause can be made (i.e. idiopathic or secondary), this distinction is not so evident in many clinical materials, and can also be debated in practical classification.

1.4. Pathophysiology

The etiology of iNPH is unknown. The pathophysiology of iNPH also remains to a great degree unknown. A number of theories have been launched, but there is presently no unifying theory regarding the pathophysiology of iNPH. In the original report, the main pathological principle was explained by the so called Hydraulic press hypothesis (17). According to this hypothesis, since the total force exerted on the ventricular wall represents a product of pressure times surface area, a given pressure will exert a greater force in a large ventricular system than in a small one, producing symptoms at a lower pressure level in large ventricles than in small ventricles (17). The later theory by Hakim (76) proposed the model of the brain as a sponge, where large transmural pressure differences between the subarachnoid space and the ventricles cause ventricular enlargement by squeezing water out of the brain parenchyma. These hypotheses, however, cannot explain many aspects of the condition, such as the finding that the size of the ventricles is inversely correlated to ICP in hydrocephalic patients (77), that no transmantle pressure gradient can be found in non-acute hydrocephalus (78), that persisting post-poperative ventriculomegaly does not exclude significant clinical improvement (79) and that the opening pressure of the cerebrospinal fluid does not correlate with the clinical severity in NPH-patients (80). More recent theories incorporate a more complex understanding of the intracranial pressure conditions, taking into account the dynamic nature of the ICP. A unified and omnipotent theory for the pathophysiology of NPH has anyhow yet to be proposed, and must be able to explain both the ventricular enlargement and the development of the clinical symptoms, as well as the clinical improvement after shunting. Theories have ranged from the abovementioned pure mechanical compression of the brain resulted by the dilated ventricles (76), inability to clear toxic metabolic products from the CSF as a result of decreased CSF turnover (81;81-83), congenital or early acquired hydrocephalus becoming symptomatic in late adult life (84-86), and increasing arterial pulse amplitude causing large ICP pulsations and leading to secondary parenchymal intracranial damage, the so called “water hammer” theory (87-90).

The pathophysiological basis of the motor symptoms in NPH is not completely understood. The enlargement of the cerebral ventricles has been proposed to lead to affection of the upper motor neuron fibers passing through the medial part of the corona radiata (42). This affection might be partly mechanical, by stretching of the fibers, but also ischemic changes

leading to axonal injury might play an essential role (91). Disturbances in basal ganglia pathways may have a role in both the gait and cognitive symptoms, as shown in a recent position emission tomography study (92), possibly especially affecting the pathways from the substantia nigra and basal ganglia to the frontal lobes (93). Frank compression of brainstem structures such as the pedunculopontine nucleus might also contribute, as shown a study where the degree of increase in midbrain volume following shunting correlated with clinical improvement (94).

The basis and neuroanatomical localization of the pathophysiological processes leading to the urinary symptoms are even less understood. As previously cited, urodynamic studies show evidence of detrusor hyperactivity (51), and the indifference towards the incontinence in late stages may indicate frontal executive dysfunction (35).

The cognitive symptoms in NPH are diverse, as previously shown, but point towards a subcortical dementing process (54). The neuroanatomical basis for this is unclear, but some authors argue that a dysfunction in the frontostriatal system is probable (42).

It is becoming increasingly evident that NPH shares common pathological features with other degenerative diseases of the CNS. It has been shown that there is a high occurrence of Alzheimer-like changes in the cortex of NPH-patients (95-98). It has hence been speculated whether Alzheimer's disease and NPH might have a common pathophysiological basis (81), and later studies have shown that the protein pattern in the CSF of NPH patients is similar to the protein pattern in Alzheimer's disease (99). Nevertheless, CSF-shunting in Alzheimer's disease has so far shown no benefit (100). NPH also has a strong relation to cerebrovascular disease (101;102), and it has been postulated that subcortical arteriosclerotic encephalopathy, or vascular dementia, might be pathophysiologically related to both NPH and Alzheimer's disease (88;103;104). It has also been shown that NPH might present as a shunt-responsive type of parkinsonism (50). All these features points to a complex interaction between CSF dynamics, cerebral blood flow, brain metabolism and senescent physiological changes.

1.5. Epidemiology

Little is known about the epidemiology of NPH. Table 1 in Paper I summarizes the epidemiological studies until the year 2007, citing studies that have reported a prevalence ranging from 5.38 % of the total dementia population to 0.41 % of all individuals >65 years of age, and an incidence ranging from 2.2/million/year to 18/million/year. Two more recent population based studies from Japan found, respectively, a prevalence of 2.9 % in the age group >75 years (105), and a prevalence of 1.4 % in the age group >65 years (106). The variations in the estimates for prevalence and incidence in all the cited studies probably reflects very varying diagnostic criteria, ranging from a lack of definition of NPH (71) to strict classification according to response to shunt treatment (68). The problems of clear-cut classification, as discussed in sections 4.2.4 and 4.3, adds to the difficulties of reliably assessing the epidemiology of the condition. For further discussion on this point, see section 5.1.1.

Considering the frequency of surgery for iNPH, there are likewise scarce data. In a study by Tisell, Høglund et al, the total incidence of surgery for adult hydrocephalus in Sweden varied from 2.3 to 3.6/100 000/year between regions during a three year period (107). Even though the Swedish study was not designed to study the incidence of operations for iNPH alone, iNPH was listed as cause for operation in 243 out of a total of 891 operations, making it possible to calculate an incidence of surgery for iNPH of 0.91/100 000/year.

1.6. Methods of assessment

The lack of cardinal signs that can clinically distinguish the condition from other afflictions of the elderly, together with the incomplete comprehension of the patophysiology, points to the need for information from supplemental tests. These are discussed in the following sections.

1.6.1. Radiology

Already early studies showed that assessing structural changes on CT-scans is of little prognostic value concerning the clinical response to shunting in NPH (108). Later studies have confirmed this (109;110), one also showing that the degree of clinical improvement after shunting does not correlate with the decrease in ventricular size (111). Magnetic resonance imaging (MRI) permits more detailed morphological evaluation of the intracranial compartment. MRI-studies have shown that the diameter of the corpus callosum decreases in many cases of iNPH (112). The callosal angle may be increased in iNPH, and perihippocampal morphological features may help in distinguishing ventriculomegaly secondary to cerebral atrophy from the ventriculomegaly in NPH. Nevertheless, no study has shown added diagnostic value of these supportive findings (42). The aqueductal CSF flow velocity have been shown to be higher in NPH patients (113), but studies have not been able to show a significant correlation between the flow velocity and response to shunting (114;115).

1.6.2. CSF tap test

In the original report by Hakim and Adams (17), 15 ml of CSF was removed by a spinal tap from each of the three patients, leading to a marked clinical improvement. A general problem is the lack of universally applicable criteria for improvement after performance of a tap test. Nevertheless, this easy test is still widely used for the diagnosis of NPH, although the removal of larger volumes, i.e. 40-50 ml is now generally advocated (116). Several studies concerning the prognostic value of this diagnostic tool have been conducted (65;117-120), and a summary of the referred studies concluded that the positive predictive value of this test is good, while the negative predictive value probably is poorer, suggesting that many patients who would benefit from shunting would be missed using a negative tap test as an exclusion criterion (116).

1.6.3. External lumbar drainage (ELD)

The ELD consists, in line with the original report (117) of inserting a lumbar catheter and draining 10 ml of CSF per hour for 72 hours. No studies have assessed whether this is the most efficient volume and duration. In several studies patients have been elected for ELD on the basis of a negative tap test (117;118), making the sensitivity of the ELD probably underestimated. However, the positive predictive value, judging from these studies, as well as studies by Malm et al (65), McGirt et al (53) and Marmarou et al (41), is considered to be high, probably averaging 85% (116). The complication rates are ranging from 5 to 20% (118;121;122). In many centers, ELD is considered the gold-standard of recruiting patients for surgery. ELD requires, however, that the patients are hospitalized for several days in highly specialized departments, and it is therefore a cost-demanding procedure. As with the tap test, a general problem is the lack of universally applicable criteria for improvement.

1.6.4. Cisternography

The procedure consists of injecting an isotope (usually ^{131}I-labeled serum albumin or IN-111 pentetate) into the lumbar subarachnoid space, and performing subsequent intermittent gamma-imaging during 24 or 48 hours. Ventricular reflux and delayed ascent over the cerebral convexities were supposed to be the hallmarks of the NPH-patient. This procedure is still used in some, albeit few, centers. The only clinical study to assess the prognostic value concludes that cisternography do not improve the diagnostic accuracy of combined clinical criteria and CT-criteria (123).

1.6.5. Hydrodynamic measurements

The lumbar infusion test was originally described by Katzman and Hussey (124). In the Katzman infusion test, an isotonic solution is infused at a constant rate via a needle placed in the lumbar subarachnoid space (see also section 3.2.1). Traditionally, the resistance to outflow (R_{out}) is defined as the difference between the reached plateau level of pressure and the opening pressure, divided by the infusion flow rate. Several other infusion methods exist, including the bolus method (125), the constant pressure method (65) and the

ventriculocisternal method (126). Most studies have been conducted using variants of the original Katzman test, which generally produces higher values of R_{out} (116). Several studies have addressed the predictive value of R_{out} (43;65;109;120;126;127). The results, as to prediction of outcome after shunting, are very diverging, probably reflecting center- and examiner-specific variations, different diagnostic and clinical criteria, as well as the fact that many series have not differentiated between iNPH and sNPH. Thus, two systematic reviews have concluded that the results are center-specific, one citing that the only class II prospective study (65) found marginal sensitivity, specificity and positive predictive value (116), the other concluding that the use of R_{out} determination has "questionable value" (36).

The value of measurement of the single wave pressure amplitude from the lumbar infusion test is discussed in detail in subsequent sections of this thesis.

Intracranial assessments of hydrodynamic parameters have also been extensively studied. B-waves; rhythmic oscillating increases in ICP lasting 0.5 to 2 minutes (15), are frequent in hydrocephalus (128-130). Several studies have reported that frequent occurrence of B-waves predict a positive outcome of shunting (128;129;131). The identification of B-waves might, however, be difficult and observer-dependent (132;133). One study found that the lumbar puncture opening pressure had no correlation with the frequency of overnight B-waves in hydrocephalic patients (134), and one study incorporating objective B-wave analysis concluded that B-waves were only weakly related to the degree of post-surgical improvement (135).

The intracranial compliance can be defined as the ability of the intracranial compartments to accommodate a volume change (136). Intracranial compliance is significantly decreased in both acute and chronic hydrocephalus (137-140), as well as in normal aging (139). This reduces the ability of the brain to dampen arterial pulse pressure waves (137), and experimental and clinical studies have shown high pulsatility in the ventricular CSF of hydrocephalic patients (141-145). Studies have also shown that single ICP wave amplitudes probably more reliably predict intracranial compliance than mean ICP alone (146;147). The importance of these observations is further detailed in subsequent sections of this thesis.

1.7. Selection of patients for surgery

Surgical treatment options in NPH-patients include placement of a CSF-diverting shunt from the cerebral ventricles to either the peritoneum (ventriculoperitoneal (VP)-shunt) or the atrium (ventriculoatrial (VA)-shunt), a CSF diverting shunt from the lumbar subarachnoid space to the peritoneum (lumboperitoneal (LP)-shunt) and endoscopic third ventriculostomy. There are insufficient data to show an advantage or disadvantage of ventricular versus lumbar shunt placement (148). There is one retrospective study comparing VA- and VP-shunts in hydrocephalic patients, finding no difference in complication rates (149). A recent multicenter study showed that endoscopic third ventriculostomy might be effective in iNPH (150), but a wider use of this procedure is still not advocated in NPH-patients (151), still making a VP- or VA-shunt the mainstay of surgical treatment (148). Interestingly enough, no randomized controlled trial has yet assessed whether placement of a shunt is effective in NPH, as shown by a Cochrane review (152).

A single standard for the prognostic evaluation of NPH patients does not exist. From the discussion in sections 1.2.4 and 1.6, it is clear that the selection of the individual patient for surgery must rely on information from multiple domains. In line with this, a review indicated that maximum 50% of patients with clinical and radiological iNPH respond to shunt treatment (36), showing that supplemental tests to help identify patients who will respond favourably to shunting are needed. The Guidelines for the diagnosis and management of iNPH from 2005 thus recommended a five step procedure, aiming at a degree of certainty for improvement of >80%. This procedure incorporates clinical evaluation, supplemental testing in the form of CSF-tap test and/or determination of R_{out} and, in cases of subsequent doubt, ELD (116).

As outlined in sections 1.6.1 through 1.6.5, no single test can to date predict with a high both positive and negative predictive value who will benefit from shunting. This adds to the fact that the clinical features alone likewise are not able to predict the shunt response, as shown in sections 1.2.1 through 1.2.4. The lack of a single uniform prognostic test and/or clinical feature is reflected in the fact that practice to confirm the diagnosis and to select patients for surgery varies widely (36;153).

The key symptoms of iNPH, problems with gait, urinary continence and cognition, are abundant in the elderly, and are rather indeterminate. Studies have shown that patients having potentially shunt-responsive iNPH can present with only one or two of the symptoms in the clinical triad (42;80), and that a variety of symptoms can be associated with the condition (49;50;154-156). The lack of epidemiological data concerning the occurrence of iNPH therefore also poses a problem when trying to select patients for both diagnosing and treating iNPH.

As previously stated, using the degree of shunt response as a diagnostic criterion for iNPH is problematic and can be viewed as something of a tautology. When selecting patients for surgery, one must therefore bear in mind that there is an obvious difference between diagnosing iNPH per se on the one hand, and predicting who will benefit from shunting on the other. Considering the age group in question, some patients will have co-morbid conditions hampering an otherwise good clinical response from shunting. Furthermore, the pathological process might have progressed to a stage where the patient is refractory to treatment (116). These features point to the need for careful interpretation when assessing shunt response rates from clinical studies.

For the practicing neurologist facing patients in whom iNPH might be a possible differential diagnosis, all the above mentioned aspects are a source of confusion: In whom, and how often, should I consider the possibility of iNPH? How should iNPH be diagnosed? Which patients should be referred to surgical treatment?

2. Aims of the thesis

The aims of the thesis were as follows:

- To estimate the epidemiology of iNPH in a Norwegian population compared to the incidence of surgery for the condition.
- To assess whether lumbar measurements of cerebrospinal fluid pressure concurs with intracranial measurements, and with the clinical response to shunting.
- To assess which of the lumbar hydrodynamic measurements that best can predict the clinical response to shunting.

3. Methods

3.1. Epidemiology

3.1.1. The Vestfold study of iNPH (Paper I)

Patients from the Norwegian county of Vestfold were included in this study. Starting two months before the 12 months inclusion phase, we actively and systematically informed about iNPH to all the county's institutions and health practitioners. They were asked to refer "any patient, irrespective of age, having a history of at least three months of gradually increasing gait and/or balance problems with concomitant subjective impairment in cognition and/or urinary symptoms" (Paper I). We also aimed to inform the public, using entries about iNPH in local newspapers, radio shows, news broadcasts, and the local television channel.

All patients underwent detailed neurological clinical assessment performed by the main investigator (AB), and were included if they fulfilled the following criteria: "A history of at least three months, not entirely attributable to other conditions, of gradually increasing disturbance in gait and balance with concomitant urinary incontinence or urgency and/or subjective cognitive impairment as experienced by patient and/or family" (Paper I).

All patients underwent CT or MRI to assess the existence of ventricular enlargement. In all the included patients, a lumbar puncture was performed, followed by a lumbar infusion test. The patients were retrospectively classified into the categories *Probable, Possible* or *Unlikely iNPH*, using the *Guidelines for the diagnosis and management of iNPH* (42).

The prevalence and incidence rates were calculated using the population figures for Vestfold and Norway from Statistics Norway's StatBank (157). The study was approved by the Norwegian social science data services and by the Regional Committee of Ethics.

A search was performed in MEDLINE, identifying papers with the term "normal pressure hydrocephalus", combined with the terms "epidemiology", "prevalence" and "incidence". EMBASE was likewise searched, looking for papers with the subject heading "normotensive hydrocephalus" and the subheading "epidemiology". In relevant studies

(26;68;71;153;158) the reference lists were examined, looking for additional relevant studies.

3.1.2. The national incidence of surgery for iNPH (Paper II)

In Norway's five neurosurgical regional centers, the authors of this paper personally collected information about all patients who, during the period from 2002 to 2006, had been "hospitalized with any diagnosis of iNPH and operated with insertion of a ventriculo-peritoneal or ventriculoatrial shunt system, or with endoscopic third ventriculostomy" (Paper II). The patients were identified by using the computerized patient journal registry at each center, automatically searching for the relevant diagnostic codes and operation codes. To verify the diagnosis of iNPH, a manual search was performed by the authors at each center and in all patient records. The placement of a shunt system or the performance of a third ventriculostomy was also verified. Patients who only underwent shunt revisions were excluded. Information about age, sex, operation year and operation type were collected. The Norwegian social science data services approved the study. The Regional Committee of Ethics was informed, and had no objections to the study. Prevalence and incidence rates were calculated using population data from Statistics Norway's StatBank (157).

3.2. Methods of assessment

3.2.1. The concurrence of lumbar CSFP with ICP (Paper III)

Lumbar CSFP and ICP data were collected from 27 consecutive iNPH patients. Overnight ICP monitoring was performed, followed by a lumbar infusion test, in which simultaneous recordings of lumbar CSFP and ICP were taken. Raw data were sampled at 100 or 200 Hz, and stored on a computer server. They were analyzed retrospectively, using a method previously described (159-161). This method includes software that automatically detects pressure peaks and valleys, based on the units "with" (time in seconds) and "threshold" (ICP in mmHg). For details regarding the calculations applied in this software, see reference 160.

This method automatically identified the cardiac-beat induced pressure waves, removing pressure waves caused by artifacts in the pressure signals due to noise. Simultaneous pressure waves in the lumbar CSF and the intracranial compartment obtained during infusion were then compared (162). The pulse pressure amplitude, latency and mean single wave pressure were computed for every cardiac beat-induced single pressure wave (159-161).

In consecutive 6-seconds time windows, mean lumbar CSFP wave amplitude and mean ICP wave amplitude, as well as mean values of mean single wave pressure (i.e. mean lumbar CSFP or mean ICP) were computed (159;160).

The lumbar CSFP-resistance to CSF outflow (CSFP-R_{out}) and the ICP-resistance to CSF outflow (ICP-R_{out}), were computed for each lumbar CSFP and ICP recording during lumbar infusion testing (163;164).

Agreement between average values of mean CSFP wave amplitude and mean ICP wave amplitude, mean CSFP and mean ICP, and between CSFP-R_{out} and ICP-R_{out} were examined and determined using a Bland Altman plot (165).

We also examined whether elevated lumbar mean CSFP wave during lumbar infusion could predict elevated mean ICP waves during long-term, overnight ICP monitoring. We defined lumbar mean CSFP wave amplitudes as elevated when they were "either $\geq$7 mmHg in 60% of time, $\geq$8 mmHg in 30% of time or $\geq$9 mmHg in 10% of time" (Paper III), and mean ICP wave amplitudes as elevated when they were "either $\geq$4 mmHg in 70% of time, $\geq$5 mmHg in 40% of time or $\geq$6 mmHg in 10% of time" (Paper III).

3.2.2. The concurrence of intraparenchymal pressure with intraventricular pressure (Paper IV)

The study presented in Paper IV was undertaken to explore whether pressure signals obtained from the ventricular CSF and the brain parenchyma gave comparable results, as related to identification of cardiac-beat waves. This study used the same sensors as used in the papers III, V and VI.

The intracranial measurements were performed on a 48-year-old man with subarachnoid hemorrhage (SAH) from a left middle cerebral artery (MCA) aneurysm. He was treated in the intensive care unit, The National Hospital, Oslo, were he immediately after arrival received an external ventricular drainage (EVD) and an ICP-sensor along this drainage. The day after arrival, he underwent craniotomy and aneurysm clipping. He was extubated and awakened the subsequent day.

The EVD was left in place during the next few days, during which simultaneous ICP monitoring from the CSF and the parenchyma (PAR) was performed intermittently. The EVD was closed for CSF drainage during the CSF/PAR pressure monitoring.

3.3. Selection of patients for surgery

3.3.1. The lumbar infusion test and clinical response to shunting (Paper V)

During a period of 12 months, all patients referred for suspected iNPH to the County hospital of Vestfold, Norway, were included in this study. The algorithm for patient management is described in section 3.1.1, as well as in further detail in Paper I. Patients were categorized into either *Possible* or *Probable* iNPH (42).

A NPH grading scale was used to clinically grade all patients and evaluate outcomes (166). This grading scale assesses gait disturbance, dementia and urinary incontinence, each ranging from 1 to 5, giving a total range from 3 to 15. All patients had a CT or MRI of the brain, and a standardized lumbar infusion test. The resistance to CSF-outflow (R_{out}) was determined from the variables opening pressure (Po) before infusion and plateau pressure (Pp) during infusion. The R_{out} was calculated as (Pp – Po)/infusion rate (125), see also section 1.6.5.

The CSFP pulsatility (CSFP-Q_{pulse}) was calculated retrospectively as described in section 7.2.1, and the mean CSFP wave amplitude was computed

Patients with *Possible* or *Probable* iNPH and R_{out}> 10 mmHg/ml/min, were referred to the Department of Neurosurgery, The National Hospital. According to this departments own

routines (167), some of the patients were selected for surgery, and received an extra-cranial programmable valve shunt with opening pressure 10-14 cm H_2O.

Neurological assessment was performed in all shunted patients, and in a subgroup of 12 age- and sex-matched non shunted patients, after 12 months.

The regional human research committee and the Norwegian social science data services approved the study.

3.3.2. The lumbar infusion test versus ICP and clinical response to shunting (Paper VI)

All patients who had been examined for suspected iNPH with over-night ICP monitoring and lumbar infusion testing in the Department of Neurosurgery, The National Hospital, Norway, from 2002 until 2007 where included in this study. The criteria for surgical treatment (implantation of a VP-shunt) were as described in an earlier paper (168), and consisted of a combination of clinical and radiological observations and ICP monitoring.

The patients had their first follow-up after three months, and the shunt response was evaluated after 12 months. CSFP was determined as the average of CSFP wave amplitude during the opening phase after lumbar puncture, and as the average of CSFP wave amplitude during 10 minutes of infusion at a rate of 1.5 ml/min.

The study was approved by the local hospital authorities, as well as by the Norwegian Social Science Data Services. The Regional Committee for Research Ethics was informed, and had no objections.

4. Results

4.1. Epidemiology

4.1.1. The Vestfold study of iNPH (Paper I)

Eighty-six patients were admitted to the study. 81 out of these were included. Nine out of the 81 had no urinary or cognitive symptoms; and eight had other conditions explaining their symptoms. In 63 patients, neuropsychological and radiological assessment as well as lumbar puncture was performed. Lumbar puncture was not technically possible in one patient.

The diagnostic criteria of *Probable* iNPH were fullfilled in 48 patients; 25 men and 23 women. The prevalence of this diagnosis then was 21.9/100,000. On the time of inclusion, 12 out of these 48 patients had had their symptoms for less than one year. The incidence could thus be calculated to 5.5/100,000/year.

The diagnostic criteria of *Possible* iNPH were fulfilled by all the 63 patients. Hence, the prevalence could be calculated to 28.7/100,000. Out of the 63 patients, 16 had had their symptoms for less than one year, Hence, the incidence could be calculated to 7.3/100,000/year.

The prevalence of iNPH showed age dependency. In the age group >65 years, the prevalence of probable iNPH was 3.3/100,000. In the age group 70-79 years, the prevalence was 181.7/100,000. In the age group < 80 years, the prevalence was 93.3/100,000.

Our literature search identified four original epidemiological studies in the field of NPH. In these studies, the estimated incidence ranged from 0.2 to 1.8/100,000/year, while the estimated prevalence ranged from 0.41% in the total population >65 years to 5.38% of the demented individuals in the population.

4.1.2. The national incidence of surgery for iNPH (Paper II)

During the five year period, 252 patients were operated. Hence, the total incidence could be calculated to 1.09/100,000/year, ranging from 0.84/100 000/year in 2006 to 1.47/100,000/year in 2004. There was no clear trend to whether the number of operations increased or decreased during the five years period. Eight ventriculostomies were performed in South-East. With that exception, no significant relations between sex, region, type of operation and yearly total number of operations could be identified. The five year incidence was highest in the age group 70-79 years, reaching 52.1/100,000.

4.2. Methods of assessment

4.2.1. The concurrence of lumbar CSFP with ICP (Paper III)

35,532 CSFP/ICP single wave pairs were available for analysis in the 27 infusion tests performed in this study. Pulse pressure amplitudes of CSFP waves were lower than for ICP waves in the vast majority of these wave pairs, with a mean difference of –2.14 mmHg. Mean difference in mean single wave pressure was 1.5 mmHg, but the variation was large. The mean difference in latency between all CSFP and ICP wave pairs was 0.04 seconds. The latency values were longer for CSFP than for ICP single waves.

The mean CSFP wave amplitude and the mean ICP wave amplitude during lumbar infusion correlated strongly. The average values of trend plots of mean CSFP wave amplitude and mean ICP wave amplitude had a mean difference of –2.5 mmHg, while the mean CSFP wave amplitudes always were lower than the corresponding mean ICP wave amplitudes.

The mean CSFP and the mean ICP correlated strongly, while the differences were large between the mean CSFP and the mean ICP during infusion. The CSFP-R_{out} and the ICP-R_{out} during lumbar infusion testing also correlated strongly.

When performing Pearson correlations, we found that the CSFP-derived parameters during lumbar infusion and ICP-derived parameters during long-term ICP monitoring only correlated strongly between mean CSFP wave amplitude and mean ICP wave amplitude. The mean ICP wave amplitude correlated only weakly with the mean CSFP, and not with the CSFP-R_{out}.

A multiple regression model showed that during lumbar infusion, only the mean CSFP wave amplitude related significantly to mean ICP wave amplitude recorded during long-term ICP monitoring.

The presence of elevated mean CSFP wave amplitudes was related to elevated mean ICP wave amplitudes during long-term ICP monitoring in 21 out of the 27 lumbar infusion tests (78%).

4.2.2. The concurrence of intraparencymal pressure with intraventricular pressure (Paper IV)

218,589 CSF/PAR single wave pairs from this patient were analyzed. There was a marginal mean difference in pulse pressure amplitude between the CSF/PAR wave pairs (–0.13±1.1 mmHg). The difference in single wave mean pressure was –0.71±6.8 mmHg, while the difference in latency was only -0.01±0.09 seconds.

4.3. Selection of patients for surgery

4.3.1. The lumbar infusion test and clinical response to shunting (Paper V)

Eighty-six patients were referred for tentative iNPH. Lumbar infusion testing was performed in the 63 patients that fulfilled the criteria of *Possible* and *Probable* iNPH (see section 3.1.1).

The infusion test-derived parameters R_{out} and Q_{pulse} related weakly in the 63 lumbar infusion tests. R_{out} could not predict which lumbar infusion tests that had abnormal CSFP-Q_{pulse}. R_{out}

and percentage of 6-s time windows with mean CSFP wave amplitude being either ≥5 mmHg, ≥6 mmHg, ≥7 mmHg, ≥8 mmHg or ≥9 mmHg correlated significantly, but R_{out} was not predictive for which lumbar infusion tests that had abnormal CSFP-Q_{pulse}.

Abnormal hydrodynamics during lumbar infusion was shown only in some of the patients with *Possible* and *Probable* iNPH. Between the two groups, the levels of R_{out} and CSFP-Q_{pulse} were not significantly different. No significant correlation was found between clinical severity and lumbar infusion test results, between R_{out} and total NPH score, or between Q_{pulse} and total NPH score.

Continuous over-night ICP monitoring showed abnormal ICP-Q_{pulse} in 23 of the 32 patients referred to neurosurgery (72%). 20 out of these 23 patients were shunted, while three rejected shunt treatment The shunted and the non-shunted patients did not differ in baseline characteristics.

Shunt treatment had a 15% complication rate in this material. 3 patients were dead at the time of neurological follow-up after 12 months. None of these died of causes related to management. 16 out of the 18 shunted patients (89%) had improved neurologically at the 12 months follow-up. The non-shunted patients were unchanged or worse.

Shunt response was highly related to CSFP-Q_{pulse} during lumbar infusion, but not to R_{out}. No correlation between R_{out} and change in NPH-score was found after 12 months, but CSFP-Q_{pulse} during lumbar infusion and change in NPH score after 12 months correlated significantly. Spearman's correlations were significant for change in NPH score versus percentage of 6-s time windows with mean CSFP wave amplitudes ≥5 mmHg, ≥6 mmHg, and ≥7 mmHg in the shunted patients.

Clinical improvement was not related to the presence of co-morbidity. After 12 months, all patients with abnormal preoperative CSFP-Q_{pulse} had a very significant shunt response. A very good shunt response was also present in five of the patients with normal CSFP-Q_{pulse} during lumbar infusion. An abnormal ICP-Q_{pulse} during continuous ICP monitoring was present in all these. Lumbar infusion testing hence did not reveal abnormal pulsatility predictive of clinical improvement after shunting in 5 out of 32 patients (16%).

Only one out of the 17 patients that had abnormal ICP-Q_{pulse} during ICP monitoring did not improve in NPH-score after 12 months. This patient was later diagnosed with progressive

supranuclear palsy. Thus, quantification of the ICP pulsatility (ICP-Q_{pulse}) was more strongly related to change in NPH-score than the results of infusion testing.

4.3.2. The lumbar infusion test versus ICP and clinical response to shunting (Paper VI)

A total of 62 iNPH patients were included, and underwent lumbar infusion testing the day following over-night ICP monitoring. There were minor complications from diagnostic ICP monitoring in 4 of 62 patients (6.5%). No patients had complications from the lumbar infusion test.

All patients had a normal static ICP, while ulsatile ICP was elevated in 42 of 62 patients (68%) during over-night ICP monitoring. Pulsatile CSFP was low in 17 out of these 42 patients during the opening phase of lumbar puncture, but low in only 5 subjects during infusion.

Shunting was performed in 45 patients. 78% were shunt responders. 18% had major complications after shunting. 13% had minor complications. 44 out of the 45 patients had an $R_{out} \geq 12$ mmHg/ml/min. R_{out} and clinical improvement 12 months after shunting correlated weakly, but significantly.

Clinical improvement 12 months after shunting and pulsatile ICP recorded over-night correlated highly significant. Clinical improvement did not, however, correlate with the pulsatile CSFP during the opening phase after lumbar puncture. Change in NPH score after 12 months and pulsatile CSFP measured during lumbar infusion correlated significantly. Shunt responders and non-responders were differentiated by the CSFP pulse during the opening phase after lumbar puncture. They were even better differentiated by the CSFP pulse during infusion, and best differentiated by the over-night ICP-monitoring.

Predicting shunt response from the pulsatile ICP recorded over-night, and from pulsatile CSFP during lumbar infusion both gave high positive and negative predictive values (PPV and NPV).

5. Discussion

5.1. Epidemiology

5.1.1. The Vestfold study of iNPH (Paper I)

As discussed in the paper, having only one neurological and one neurosurgical department to serve the Vestfold County makes it highly possible that there has been no leakage of patients to other hospitals, especially since all the counties that surround Vestfold admit their neurosurgical patients to the National Hospital as well. As shown in the paper, Vestfold County did not differ from the rest of Norway on a few major parameters. The ethnic homogenicity and high geographical mobility in Norway also adds to the high probability that the findings in the study can be extrapolated to the whole of Norway. Nevertheless, one must bear in mind that the etiology of iNPH is unknown, extrapolating the findings to populations in other parts of the world must therefore be done with care.

The study was population based, accepting patients directly from homes and nursing homes. This is not the case with most of the few other epidemiological studies that has been performed in this field. The study by Vanneste et al (68) was retrospective, including only patients admitted to neurosurgical centres and treated with shunt insertion. Using these criteria, and furthermore including only patients who also had a good response from their shunt insertion, they calculated an incidence of 2.2/million/year. Using this design, the prevalence could not be estimated. Krauss and Halve's study (153) was a questionnaire survey of 82 neurosurgical centres in Germany, out of which 65% responded. The estimated annual incidence of NPH was 1.8/100,000. It is not clearly defined in the questionnaire whether shunt insertion and shunt response was necessary to confirm the diagnosis, and the diagnostic criteria varied from centre to centre.

In contrast to these two neurosurgical materials stands Trenkwalder et al's study from 1995, where 982 out of a total population of 1192 inhabitants over the age of 65 years in two German villages were examined for Parkinsonism (158). A total of 45 showed clinical signs of Parkinsonism (i.e. basal ganglia signs). Out of these, 4 patients were diagnosed as having NPH, making the prevalence in this study 0.41% in the age group over 65 years of age. In

contrast, the prevalence of iNPH in our study was 0.12% in the age group over 65 years of age (117.8/100.000). The diagnostic criteria in Trenkwalder et al's study, however, varied sligthly from ours, including "typical gait disorder, bladder incontinence, dementia to a variable extent, and corresponding periventricular lucencies with ventricular enlargement". The patients in Trenkwalder et al's study were 76, 82, 84 and 89 years of age, i.e. somewhat older than our patients, but a further analysis of differences between the two patient materials is not warranted because of the low absolute number of patients. It is worth noting, though, that one of the prerequisites for referral to our project was "gradually increasing symptoms", something that a priori probably would have excluded at least two out of the four patients in Trenkwalder et al's material, because they had had their symptoms for many years at the time of inclusion.

In Vale and Miranda's study from 2002 (71), 168 patients with dementia, all admitted to a tertiary-care outpatient clinic in Brazil from 1997 to 1999, were examined 18 months after their initial assessment. It is stated that all patients underwent CT and/or MRI, but the results of these examinations are not stated. The authors reported that 10 patients (5.4%) had NPH. The diagnostic criteria for this, however, is not stated, neither whether they showed the clinical triad, nor whether they showed ventriculomegaly on the radiological examination.

In summary, Trenkwalder et al's study (158) is the only study that can be said to have a strictly population based methodology. This methodology would theoretically yield a somewhat higher prevalence than our methodology because it is more strictly population based and not relying on referral of patients. This concurs with the fact that this paper reports a higher prevalence than ours. We found a total of 10 patients living in the county of Vestfold that had previously been shunted for iNPH. These patients were not included in the material since we did not have sufficient preoperative data to classify them according to our criteria. If, theoretically, these patients were included in our population figures, this would yield a prevalence of 0.17% in the age group over 65 years of age, something which still is below Trenkwalder et al's prevalence numbers. Still, Trenkwalder et al's primary inclusion criteria of Parkinsonism could theoretically lead to an underestimation of NPH, because Parkinsonism is not a primary trait in NPH. It is also worth noting that Trenkwalder et al's paper, Vanneste et al's (68) paper and our paper, are the only three to have a clear definition

of NPH as basis for the epidemiological estimates. Not surprisingly, comparison between these three publications shows an inverse relationship between the narrowness of the inclusion criteria and the occurrence of NPH reported.

Our methodology differs from a strict population-based methodology since the total population was not examined systematically. A strictly population based approach would, however, raise dificulties: Given the probable prevalence range of NPH, one would have to clinically assess several thousands of inhabitants to reach a fair number of NPH-patients, something that would neither be practically nor ethically feasible.

We applied wider primary inclusion criteria than any of the abovementioned studies, except Vale and Miranda (71), who did not report any inclusion criteria in their study, nevertheless only 86 out of nearly 220,000 inhabitants were admitted to our study. This might have several explanations, as elaborated on in the "Discussion" section of the paper (Paper I).

63 patients in our material underwent lumbar puncture as part of the diagnostic evaluation. 59 out of these had an opening pressure between 5 and 18 mmHg, which is the physiological criterion for the diagnosis of "Possible iNPH" according to the cited criteria (42). The four patients in our material that did not meet these criteria all had opening pressures below 5 mmHg (unpublished figures). The reason for having the upper limit of 18 mmHg is obvious, since high opening pressures are more indicative of acute or secondary forms of hydrocephalus (42). The reason for having the lower limit of 5 mmHg, however, is not evident. The Guidelines cite no scientific evidence suggesting that a low opening pressure is incompatible with the diagnosis of iNPH. Few studies report details about the opening pressure of iNPH-patients. In the Dutch NPH-study, the 101 patients were reported to have a baseline CSF-pressure mean of 11.2, with a standard deviation of 3.3 and a range from 5 to 20 mmHg (43). However, they do not report significant correlation between the opening pressure and degree of shunt response. Neither do any other of the large series of iNPH-patients. It is therefore, in my opinion, dubious whether patients with an opening pressure of for instance 3 or 4 mmHg should be any less likely to have the condition than patients with an opening pressure of 5 mmHg, However, if we had included the four patients with a lower opening pressure in our study, this would not have made any practical difference, since none of them anyhow complied with all the other criteria for the diagnosis.

It is important to notice that our study reports the occurrence of "Probable" and "Possible" iNPH (42), and not the occurrence of shunt responsive NPH. No study has thus far assessed the rate of shunt response when using these diagnostic criteria. 32 out of the patients in our study were referred to neurosurgery (see paper V in this thesis). Continuous over-night ICP monitoring showed abnormal ICP-Q_{pulse} in 23 out of these (72%). 20 were shunted, and out of the 18 who was available for 12 months follow up, 16 had improved neurologically (see paper V, as well as section 7.3.1 of this thesis). The study was not designed as to test how well the guidelines are able to foresee shunt responsiveness. No clear conclusion can hence be drawn from this, except for the fact that at least some of the patients who fulfill the diagnostic criteria of "Probable iNPH" will profit from shunt treatment.

After the publication of our study, a Japanese retrospectively analysed community-based study of 170 community dwelling subjects of > 75 years of age has been published (105). In this material, 2.9 % showed radiological and clinical features consistent with iNPH. The authors in this study did not, however, perform lumbar puncture. The diagnostic criteria used were the diagnostic iNPH-criteria from the Japanese Society of NPH (169), and not the same guidelines that were used in our study (42). Another recent Japanese study randomly selected 567 individuals from among 1654 members of a rural population aged 65 years and older. They found that the prevalence of "possible iNPH" (42) was 1,4 %. These studies again illustrate the need for more uniform diagnostic definitions in this field of study, and therefore the importance of internationally accepted guidelines. It also illustrates the need for further epidemiological studies both related to the epidemiology of the condition by itself, and to the response to shunt treatment.

5.1.2. The national incidence of surgery for iNPH (Paper II)

As described in section 3.1.2, the data in this study were collected by using the computerized patient journal registry at each center, automatically searching for the relevant diagnostic codes and operation codes. As step two, a manual search was then performed by the authors at each center and in all patient records indicated by the computerized patient journal registry. In Norway's health care system, part of the economic compensation given

from the health care authorities to the individual hospital is linked to the number of patients treated (i.e. the diagnoses of the individual patient) and to the number of surgical procedures performed in the hospital. Because of this system of reimbursement, the hospitals give much effort in keeping the data files of diagnoses and surgical procedures as complete as technically possible. This makes it highly possible that step one of our strategy; the use of the computerized patient journal registry at each center, ensured a near completeness of the data collected. Step two of the strategy; the manual search in every relevant patient record, ensured that no patient or operation was wrongly accounted for. However, this type of retrospective strategy has the disadvantage of being entirely reliant on correct coding at each center. Systematic differences in coding practice between the hospitals could theoretically give systematic errors in the data collected. Our results, however, showed that there were little differences between each regional center concerning the type and frequency of operations. This makes it less probable that there were any such systematic error in one or more of the centers. Theoretically, since the number and type of diagnoses and procedures have economic consequences for each hospital, the number of operations could have been exaggerated for economic reasons in one or more of the centers. However, our manual search of each relevant patient record makes it much less probable that this has happened.

It is interesting to note that the age dependent peak five year incidence is in the age group 70 – 79. This is consistent with our findings in Paper I, where we found the yearly incidence of iNPH to be twice as high in this age group compared to people older than 79 years (170). It is uncertain whether this reflects a true decrease in the incidence in the highest age group, or whether it merely reflects an age dependent selection bias in our material.

Ventricuoperitoneal shunt was the preferred operation type at all the regional centers. On eight patients in the south-east region a third ventriculostomy was performed. These procedures could be regarded as experimental treatment; four of the eight patients later received a ventriculoperitoneal shunt.

There is limited knowledge about the frequency of surgery for iNPH. In one study, the total incidence of surgery for adult hydrocephalus varied from 2.3 to 3.6/100 000/year between regions in Sweden during a three year period (107). Even though the study was not designed to study the incidence of operations for iNPH alone, iNPH was listed as cause for operation in 243 out of a total of 891 operations, making it possible to calculate an incidence of

operation for iNPH of 0.91/100 000/year, which is quite similar to the findings in our study. It is somewhat surprising that the incidence of surgery for iNPH seems to be quite similar both between different Norwegian regions, as shown in our study, and between two nordic countries, as shown in this Swedish study as compared to our study. This is in spite of the lack of uniform guidelines both for diagnosing iNPH, and for choosing which patients to operate. One explanation for this could be that this reflects the true incidence of the condition, i.e. that since the incidence and prevalence of the disease is stable between regions and neighboring countries, then this is reflected in a stable incidence of surgery. However, data from Paper I in this thesis suggest that there is a minimum incidence of iNPH of 5.5/100 000/year in Norway, while Paper II showed a total incidence of surgery for iNPH of 1.09/100 000/year. As previously noted, one must bear in mind that Paper I did not report the incidence of shunt-responsive iNPH, but the incidence of "probable iNPH" (42). How many of these patients who would profit from insertion of a shunt is unknown, as prediction of shunt-response is difficult, probably depending also on independent factors such as age and duration of symptoms (31;42;148). Degree of co-morbidity has in a recent article also been shown to be a significant predictor of the quality of clinical outcome after shunt insertion (171). Even with these reservations, there is an obvious discrepancy between the probable incidence of the condition and the incidence of surgery for the condition. There are several possible explanations for this discrepancy: Firstly, the syndrome of iNPH is generally little known to the public, as opposed to many other afflictions of the elderly. Secondly, the syndrome is probably also generally little known among many general practitioners and other health care workers. There is evidence to suggest this, as the information campaign we conducted in Vestfold, Norway in the Vestfold iNPH-study (Paper I, see section 3.1.1) gave 86 referrals and resulted in a total of 20 shunted patients in one year (Paper V, see section 4.3.1), as opposed to a total of 18 shunted patients from the same region during the previous 10 years (Paper I). Thirdly, the symptoms of iNPH (gait problems, urinary incontinence and dementia) are abundant in the elderly. This means that even when given knowledge about the existence of the syndrome, it is not necessarily evident for neither patients nor health care workers when and whom to refer. Connected to this is also the fact that iNPH mostly affects an age group where unspecified, insidious symptoms often are considered inevitable or even part of normal aging (a shuffling gait might for instance be taken as part of normal aging, and not as part of a treatable syndrome).

The lack of universally accepted guidelines for diagnosing iNPH, and the lack of powerful tests to predict shunt success in the individual patient, probably also contributes to the relative low rate of surgery.

5.2. Methods of assessment

5.2.1. The concurrence of lumbar CSFP with ICP (Paper III)

An interesting observation in this study was that the intracranial pulse pressure amplitudes increased more than the corresponding lumbar cerebrospinal fluid pulse pressure amplitudes during lumbar infusion. In absolute numbers, the lumbar cerebrospinal fluid pulse pressure amplitude values were about 2 mmHg lower than the intracranial pulse pressure amplitudes. We hypothesize that this might be due to differences in compliance between the lumbar CSF and intracranial compartments. Since a previous study has showed that that the pulse pressure amplitudes increase when intracranial compliance declines (172), the raise in pulse pressure amplitude may represent the pressure response to the increase of intradural volume during lumbar infusion. A less increase in the lumbar cerebrospinal fluid pulse pressure amplitudes may therefore indicate that the compliance capacity is higher within the lumbar CSF compartment than within the intracranial compartment. This might in part be an example of a “windkessel effect”, as seen in many pulsating biological flow systems. Nonetheless, a previous study has given evidence indicative of that the spinal compartment contributes only about one third of the total spinal/cranial compliance capacity (173). Even though this observation is not incompatible with our observation of the lower amplitudes in the spinal compartment as compared to the intracranial compartment, further studies must clarify the distribution of compliance capacity within the intrathecal compartments.

Our observation could also have been explained by the existence of a pressure gradient between the CSF and the brain parenchyma wherein ICP is measured. Even though this possibility cannot be excluded, we were in Paper IV in this thesis not able to demonstrate such a pressure gradient between ventricular CSFP and ICP (162).

There was a larger variation between the lumbar CSFP and ICP mean single wave pressures, and also a larger variation between mean CSFP and mean ICP. Even though we took care to

keep the CSFP and ICP sensors at the same height level during lumbar infusion testing, one must bear in mind that the mean pressure is relative to the atmospheric pressure. A difference in the height level between the lumbar and intracranial sensors might therefore yield false differences in the pressures measured due to differences in baseline pressure (161).

In contrast to this, pulse pressure amplitudes are relative values not relating to, or dependent on, the atmospheric pressure, since they measure the difference between the minimum diastolic and the maximum systolic pressures. The pulse pressure amplitudes are therefore not dependent on the baseline pressure.

The strong correlations between lumbar CSFP- and ICP-derived parameters during lumbar infusion concur with previous data regarding mean CSFP/mean ICP and CSFP-R_{out}/ICP-R_{out} (163), and with previous data showing a correlation between lumbar CSFP-R_{out} and mean ICP (174). A significant correlation between lumbar cerebrospinal fluid pulse pressure amplitude and mean pressure during lumbar infusion testing have also been shown by others (175), and the mean difference of 2.4 mmHg/ml/min between lumbar CSFP-R_{out} and ICP-R_{out} during lumbar infusion testing is also in line with previously reported data (163).

The strong correlations between lumbar CSFP- and ICP-derived parameters during lumbar infusion do not necessarily imply a correlation to ICP-derived parameters recorded during long-term, overnight ICP monitoring, since this is a different physiological situation. Hence lumbar CSFP-R_{out} has not been shown to predict ICP during long-term overnight monitoring, neither in iNPH (163) nor in children (176). Similarly, in one of the other papers in this thesis, neither lumbar CSFP-R_{out} nor mean CSFP during lumbar infusion were related to the parameters mean ICP and mean ICP wave amplitude derived from long-term, overnight ICP monitoring (Paper III, see section 4.2.1). In the same paper, it is shown that there is a strong correlation between mean CSFP wave amplitudes during lumbar infusion and mean ICP wave amplitudes during long-term ICP monitoring. When using the threshold levels of mean CSFP wave amplitudes (164) and mean ICP wave amplitudes (166) previously determined in the Neurosurgical Department, The National Hospital, it was previously found that elevated lumbar mean CSFP wave amplitudes were associated with elevated mean ICP wave amplitudes during long-term ICP monitoring in 21 of 27 lumbar infusion tests (78%),.

For the purpose of determining to which extent the CSFP amplitudes recorded during lumbar infusion can predict the intracranial pulse presssure amplitudes during long-term ICP-monitoring, this material of 27 patient recordings was rather small. Paper VI in this thesis elaborates further on how the CSFP pulse amplitude during lumbar infusion testing concurs with the intracranial pulse pressure amplitudes during long-term, overnight ICP monitoring (see section 8.3.2).

5.2.2. The concurrence of intraparenchymal pressure with intraventricular pressure (Paper IV)

Even though this paper reports only one case, more than 118 000 CSF/PAR wave pairs were recorded and analyzed, showing that there were marginal differences in single wave parameters when ICP was monitored continuously both within the ventricular CSF and the brain parenchyma,.

Previous papers have extensively tested that the single wave identification algorithm has a correct wave detection (160;161).

As already commented on in section 8.2.1, the pulse pressure amplitudes constitute the pressure difference between diastolic minimum and systolic maximum pressures. As such, this parameter is independent of the baseline pressure or the zero pressure level calibration of the pressure transducer.

In contrast, the mean pressure parameters, including the mean single wave pressure, are relative to the atmospheric pressure. Since zero calibration for the ICP sensor in the brain parenchyma takes place in the operating theater, subsequent mean pressures are relative to the zero pressure level at the time of implantation. On the other hand, CSF pressure monitoring allows zero calibration against atmospheric pressure at anytime, but baseline pressure is heavily affected by the placement of the sensor relative to the distal end of the EVD.

These considerations taken into account, the marginal difference in CSF/PAR pulse pressure amplitudes suggests a marginal pressure gradient between the ventricular CSF compartment and the brain parenchyma. It has previously been discussed whether there is a ventricular-

parenchyma pressure gradient which can be responsible for the enlargement of the ventricles in hydrocephalus, but a study published in Neurosurgery in 2002 finds no evidence of a transmantle pressure gradient in nonacute communicating or non-communicating hydrocephalus (78). In line with this previous report, our case report gives no indication of such a pressure gradient regarding the dynamic pressure parameters. Since continuous monitoring of single wave pulse pressure amplitudes has been found very useful for neuro-monitoring, this is a significant observation (161;177).

However, our patient had a different patophysiological situation than patients suffering from iNPH, and also the patients in the reported series from 2002 (78). The ten patients in this study had communicating and non-communicating nonacute hydrocephalus. In contrast, our patient had a more acute form of hydrocephalus, stemming from an acute subarachnoid hemorrhage (SAH). The patophysiology of hydrocephalus in general is insufficiently known. This calls for prudency in comparing hydrodynamic measurements from different forms of hydrocephalus. The presence of blood in the subarachnoid space in our patient might theoretically also *per se* alter the intracranial hydrodynamics through various mechanisms, for example through a direct "irritative" effect on blood vessels and meninges, or by altering the viscosity and flow properties of the CSF. It is also worth noticing that our patient was somewhat younger (48 years) than the average iNPH-patient, and younger than the patients in the reported series from 2002 (mean 57 years, range 20-80 years) (78).

With the abovementioned reservations, this case report showed only marginal differences in pulse pressure amplitude between single CSF/PAR wave pairs, and gave no evidence of the existence of a pressure gradient between the ventricular CSF and the brain parenchyma.

The results of this study are important regarding the data presented in Paper III. In Paper IV CSFP was measured via the EVD using a Edwards fluid filled sensor, and ICP was measured via a solid Codman ICP sensor. In comparison, in Paper III lumbar CSFP was also measured using an Edward's fluid sensor and ICP via a Codman sensor. Thus, given the results of Paper IV, it appears less likely that the differences in wave amplitude reported in Paper III are caused by different properties of the sensors used.

5.3. Selection of patients for surgery

5.3.1. The lumbar infusion test and clinical response to shunting (Paper V)

As shown in Paper I in this thesis (see section 4.1.1), 63 patients fulfilled the criteria of *Possible* iNPH (75%) and 48 patients fulfilled the criteria of *Probable* iNPH (57%) among 86 patients referred to neurological work-out for tentative iNPH. As discussed earlier in this thesis (see section 5.1.2) how many of the patients that fulfil these criteria who will respond favourably to the placement of an intracranial shunt is unknown. A previous review has indicated that no more than 50% of patients with clinical and radiological iNPH respond to shunt treatment (36). This underlines the need for supplemental tests to help identify patients who will respond favourably to shunting (116), as discussed in section 1.7. It is therefore interesting that only a proportion of the 63 patients who fulfilled the criteria of *Possible*/*Probable* iNPH had an abnormal lumbar infusion test, and that the results of lumbar infusion testing were not related to the severity of iNPH. This, and the fact that the results of lumbar infusion testing did not associate with ventricular size as assessed by the Evan's index, compares with a previous study (178).

An interesting observation is that co-morbidity did not reduce the chances of clinical improvement after shunting. This was somewhat surprising, and a study published later than this study has shown that co-morbidity can be a significant predictor of the clinical outcome after shunting (171). The reason for the diverging results might be that our patient material was rather small with regard to co-morbidity. The fact that only 20 patients were shunted, and that only 18 patients were available for follow up after 12 months also place limitations on the reliability on the other results from the study with regard to the predictability of the various parameters.

Given these caveats, the R_{out} did not predict alterations in CSFP pulsatility (CSFP-Q_{pulse}) in this material. This concurs with the observation from Paper III (179). It therefore seems like the level of R_{out} is less useful for prediction of whether CSFP-Q_{pulse} is abnormal or not.

As previously discussed, the static CSFP is relative to the atmospheric pressure and dependent on the zero pressure level, while the CSFP pulsatility is independent on these factors. Data from Paper III imply that CSFP-Q_{pulse} is a better measure of the intracranial compliance (i.e. pressure volume reserve capacity) than the static CSFP (see section 5.2.1 for a more thorough discussion of this).

The results from this study confirm that patients with abnormal CSFP-Q_{pulse} during lumbar infusion (164) or abnormal ICP-Q_{pulse} during ICP monitoring (Paper III (180)) respond well to shunting. On the other hand, these results must be interpreted with care, both taking into consideration the relative low number of patients, and the fact that no patients with a normal ICP-Q_{pulse} during ICP monitoring were shunted, leaving it unanswered whether these patients likewise could have responded well to shunting. Furthermore, all patients that were shunted in our study had a R_{out} >10, as this was the prospective selection criterion for referral to neurosurgical work-out. Therefore, the correlation between R_{out} and shunt results in this study only apply to patients with $R_{out} > 10$.

One important finding is that the lumbar infusion test was false negative regarding abnormal pulsatility and clinical improvement following shunt in 5 of 32 tests (16%). These 5 patients all had abnormal pulsatility during ICP-monitoring. We therefore believe that the false negative infusion tests with regard to the pulsatility measures were caused by technical difficulties, i.e. leakage of CSF during the infusion.

In conclusion, quantification of CSFP pulsatility (CSFP-Q_{pulse}) during lumbar infusion probably improves the ability of the lumbar infusion test to predict shunt response in the individual patient, as compared to calculation of $R_{out.}$ There remains, anyhow, a problem of false negative tests also with this quantification. Larger studies are needed to better clarify these problems, and to clarify whether the lumbar infusion test is of sufficient value in the assessment of iNPH-patients. Considering the low cost, easy access and few complications to this simple test, and considering the widespread use of the test, such studies are urgently needed

5.3.2. The lumbar infusion test versus ICP and clinical response to shunting (Paper VI)

The entire experience of managing iNPH patients using diagnostic ICP monitoring in the pre-operative work-up during the period 2002-2007 has previously been reported (168). In this study, we wanted to compare this entire cohort of iNPH-patients with a subgroup from the cohort who also underwent lumbar infusion testing as part of the preoperative assessment. This subgroup of 62 patients did not differ from the entire cohort regarding age, sex, symptom duration, severity of symptoms, ventricular size or degree of shunt response (ibid).

Pulsatile CSFP was elevated in the patients who had elevated over-night ICP pulse, and more so during the period of infusion than during the opening phase after lumbar puncture. Data from Paper III in this thesis indicate that the lumbar CSFP wave amplitudes are about 2 mmHg below the simultaneous cranial ICP wave amplitudes (see section 4.2.1). This is the background for the decision to categorize ICP wave amplitudes $\geq$4 mmHg as indicative of elevated pulsatile ICP, and lumbar CSFP wave amplitude $\geq$2 mmHg as indicative of elevated pulsatile CSFP (179;181).

The pulsatile pressures were the focus of this study, and over-night static ICP was normal in all patients. Previous studies have shown that the opening pressure after lumbar puncture does not correlate with ICP recorded over-night (179;182;183), while lumbar mean CSFP agree with the ICP across a large pressure interval (184).

The role of R_{out} in predicting shunt response is still highly disputed (43;65;116;181;185). In this series, we have considered $R_{out}\geq$ 12 mmHg/ml/min as abnormal (116;174). 44 out of 45 patients had an $R_{out}\geq$ 12 mmHg/ml/min, and 35 out of these (80%) were shunt responders. Since a $R_{out}\geq$ 12 mmHg/ml/min was not the criterion for shunting, one cannot conclude whether this parameter is predicative of the shunt response. In previous series in the literature, there seems to be a clear relationship between the level of R_{out} and the degree of shunt response, in the sense that a high cut-off level of R_{out} for accepting patients to surgery gives a high degree of shunt response, and vice versa. This can be exemplified by the Dutch

normal pressure hydrocephalus study, where a positive predictive value for a good shunt response was obtained in 100% of the patients for a R_{out} cut off level of 24 mmHg/ml/min, and a positive predictive value of 80% was reached for R_{out} cut off levels of 10 to 15 mmHg/ml/min (43).

In concordance with previous series (164;181), we found a highly significant correlation between overnight pulsatile ICP and the degree of clinical improvement seen 12 months after shunting, while the correlation between R_{out} and clinical improvement was weaker. We also found that the CSFP wave amplitude measured during lumbar infusion correlated with clinical improvement after shunting, in concordance with the observations in Paper V in this thesis (see section 7.3.1).

However, the results from Paper V show that clinical improvement after shunting was best predicted by over-night ICP (see section 4.3.1). In Paper VI, the most important observation is that CSFP pulse during lumbar infusion also could predict clinical improvement after shunting.

Quite recently a group in Rome reported their experience of using an intraventricular infusion test in 120 consecutive iNPH patients over a time span of 28 years (186). This work especially focused on the comparison between R_{out} and intracranial elastance (IE), the reciprocal of the intracranial compliance. In this work, the IE was evaluated from measuring the slope of the linear regression between the diastolic ICP values and the corresponding amplitude of each CSF pulse pressure wave. Their results are very comparable to ours, showing no statistically significant difference in mean R_{out} value between improved and unimproved cases, while an IE slope value of 0.25 clearly differentiated between improved and unimproved cases (ibid).

Figure 9 in Paper VI is based on the assumption that the CSFP pulse provides an indirect measure of the compliance (pressure-volume reserve capacity) of the intraspinal compartment. Reducing compliance increases the amplitudes (dP) (187). These amplitudes constitute the pressure response to the volume change of approximately 1 ml in the intracranial compartment (188) caused by each cardiac contraction.Lumbar infusion artificially reduces the compliance (moving to the right on the pressure-volume curve). The spinal pressure-volume curve is then shifted to the right compared to the cranial pressure-

volume curve, because compliance in the spinal compartment is higher than in the intracranial compartment (179). It is therefore necessary to infuse fluid intrathecally to reach the same amplitude values in the lumbar compartment as in the intracranial compartment. The wave amplitudes are related to compliance, but do not constitute a direct measure of the compliance (189). Elevated ICP pulse is associated with reduced intracranial compliance (172). Shunting improves compliance, and it can be hypotesized that this is the reason why elevated ICP pulse measured during over-night ICP monitoring or during lumbar infusion can predict shunt response.

An important technological advantage with the method used here is that an automatic procedure is used for identification of the cardiac beat induced waves. This quality control ensures that relevant and correct pressure waves are being studied. Since the intracranial volume change during each cardiac beat is about 1 ml (188), each cardiac-beat induced pressure wave can be considered a volume-pressure, created by the nature itself. As in all biological systems, there is some time related variation within certain limits. For this reason, monitoring is done for some time to obtain the average of many cardiac induced pressure waves to reduce the impact of time-related variation. Accordingly, when ICP monitoring is done for a long time, an overview of a huge number of pressure-volume tests (each cardiac beat induced wave being a test) is obtained.

5.4. Concluding remarks

It has been estimated that the number of people affected by dementia globally will double every 20 years to 81.1 millions by 2040 (190). This will heavily affect the burden of health care, and underlines the need for simple and low threshold diagnostic tools in the assessment of cognitive decline. When evaluating tools for diagnosing iNPH, one must also bear this aspect in mind.

Several of the studies in this thesis have shown a high PPV and NPV of ICP monitoring when assessing single wave pulsatility. This is in line with the previously cited recent Italian study (186), see section 5.3.2. The external lumbar drainage (ELD) is in many centres

considered the gold standard of the supplemental tests for iNPH, see section 1.6.3. The complication rates, however, are ranging from 5 to 20% (118;121;122), and ELD requires that the patients are hospitalized for several days in highly specialized departments. It is therefore a relatively cost-demanding procedure. A general problem is also the lack of universally applicable criteria for improvement. In line with this, the Guidelines for the diagnosis of iNPH reserves the ELD for step five in the recommended procedure for identifying shunt responsive patients (116), thus underlining the need for an easier, less cost-demanding test with a high PPV and NPV.

The performance of the lumbar infusion test and the performance of the over-night ICP monitoring represent quite different clinical settings. The lumbar infusion test can be performed in an out-patient neurological setting, is little resource demanding and has few complications. In many aspects, the lumbar infusion test can be considered a low cost, low threshold procedure. The over-night ICP monitoring, on the other hand, demands admission to a highly specialised neurosurgical department, requires in-house access to neurointensive facilities. It can thus, in comparison, be viewed as a high cost, high threshold procedure, even though the complication rate has been shown to be only 2% in a large series (191).

As shown in section 4.3.1 (Paper V), the lumbar infusion testing, however, failed to reveal abnormal pulsatility and clinical improvement following shunt in 5 of 32 patients (16%), while the ICP-monitoring revealed abnormal pulsatility in all these 5 patients. Although it can be hypothesized that the false negative infusion tests relate to technical difficulties with the infusion test, this cannot be ascertained from the present data, and anyhow points to a weakness related to the procedure. Given the value of the lumbar infusion test being a low cost, low threshold procedure, larger studies addressing these problems are needed. Such studies will hopefully be able to clarify whether lumbar infusion testing with measurement of CSFP wave amplitudes has a role in assessment of iNPH.

Paper V in this thesis aimed to see how infusion test results in suspected iNPH patients related to the clinical course and shunt response. This was done by retrospectively analyzing the lumbar infusion test from 63 consecutive patients with Possible or Probable iNPH (42) during a 12 month period. In contrast, Paper VI in the thesis assessed both diagnostic lumbar infusion testing and continuous over-night ICP monitoring in 62 patients during a 6-year period. Paper VI can thus be viewed as a broadening of the perspective from Paper V,

adding further understanding to our experience with intrathecal hydrodynamics. It is important to note that the concept of “pulse wave amplitudes” used in Paper VI corresponds to the “Q_{pulse}” in Paper V.

6. Conclusion and implications for further research

Paper I in this thesis reported a calculated minimum incidence of iNPh of 5.5/100 000/year in Norway, while Paper II showed a total incidence of surgery for iNPH of 1.09/100 000/year during a five year period. It is important to note that Paper I did not report the incidence of shunt-responsive iNPH, but the incidence of "probable iNPH" (42). How many of these patients who would profit from insertion of a shunt remain unknown. In spite of these uncertainties, there is empirical support for the notion that many more patients with suspected NPH should be considered for shunt insertion (31). The data from Paper II support this view, but it is clear that further epidemiological, population based studies, also addressing the occurrence of shunt responsive iNPH, are needed.

The data from Paper III showed that the lumbar CSFP pulse amplitudes recorded during lumbar infusion could be used to predict the ICP wave amplitudes recorded during long-term, over-night ICP monitoring. Paper IV showed that there was no pressure gradient between wave amplitudes derived from brain parenchyma and ventricular CSF. Given the results of Paper IV, it appears less likely that the differences in wave amplitude reported in Paper III are caused by different properties of the different sensors used. However, the patient material of 27 patients recordings was rather small; therefore, further research is required to even better elaborate how lumbar CSFP wave amplitudes recorded during lumbar infusion can be used to predict the ICP wave amplitudes.

The data from Paper V showed that the lumbar infusion-derived parameters R_{out} and Q_{pulse} (wave amplitude) related weakly, that shunt response after 12 months was not related to R_{out}, but was highly related to the Q_{pulse} and that false negative results of lumbar infusion testing were observed in 16% of the patients. Paper VI showed that shunt response can be anticipated in 9/10 patients with elevated overnight ICP wave amplitudes, while in only 1/10 with low ICP wave amplitudes, and that an elevated CSFP wave amplitude during lumbar infusion can be used as a screening procedure for selection of iNPH patients for shunting. However, even though measurement of lumbar CSFP wave amplitudes improves the accuracy of prediction of shunt response as compared to R_{out}, the problem of false negatives from lumbar infusion tests still seems to remain to some extent even with this

method. Larger studies addressing these problems are needed, and will hopefully be able to clarify whether lumbar infusion testing with measurement of CSFP wave amplitudes has a role in assessment of iNPH, or whether these patients should be admitted directly to intracranial measurements. Altogether, the existing data point to a potential useful role of lumbar infusion testing in assessing patients with iNPH in neurological practice.

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I

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VI

CEREBROSPINAL FLUID RESEARCH

RESEARCH Open Access

Cerebrospinal fluid pulse pressure amplitude during lumbar infusion in idiopathic normal pressure hydrocephalus can predict response to shunting

Per K Eide[1*], Are Brean[2]

Abstract

Background: We have previously seen that idiopathic normal pressure hydrocephalus (iNPH) patients having elevated intracranial pressure (ICP) pulse amplitude consistently respond to shunt surgery. In this study we explored how the cerebrospinal fluid pressure (CSFP) pulse amplitude determined during lumbar infusion testing, correlates with ICP pulse amplitude determined during over-night ICP monitoring and with response to shunt surgery. Our goal was to establish a more reliable screening procedure for selecting iNPH patients for shunt surgery using lumbar intrathecal infusion.

Methods: The study population consisted of all iNPH patients undergoing both diagnostic lumbar infusion testing and continuous over-night ICP monitoring during the period 2002-2007. The severity of iNPH was assessed using our NPH grading scale before surgery and 12 months after shunting. The CSFP pulse was characterized from the amplitude of single pressure waves.

Results: Totally 62 iNPH patients were included, 45 of them underwent shunt surgery, in whom 78% were shunt responders. Among the 45 shunted patients, resistance to CSF outflow (R_{out}) was elevated (≥ 12 mmHg/ml/min) in 44. The ICP pulse amplitude recorded over-night was elevated (i.e. mean ICP wave amplitude ≥ 4 mmHg) in 68% of patients; 92% of these were shunt responders. In those with elevated overnight ICP pulse amplitude, we found also elevated CSFP pulse amplitude recorded during lumbar infusion testing, both during the opening phase following lumbar puncture and during a standardized period of lumbar infusion (15 ml Ringer over 10 min). The clinical response to shunting after 1 year strongly associated with the over-night ICP pulse amplitude, and also with the pulsatile CSFP during the period of lumbar infusion. Elevated CSFP pulse amplitude during lumbar infusion thus predicted shunt response with sensitivity of 88 and specificity of 60 (positive and negative predictive values of 89 and 60, respectively).

Conclusions: In iNPH patients, shunt response can be anticipated in 9/10 patients with elevated overnight ICP pulse amplitude, while in only 1/10 with low ICP pulse amplitude. Additionally, the CSFP pulse amplitude during lumbar infusion testing was elevated in patients with elevated over-night ICP pulse amplitude. In particular, measurement of CSFP pulse amplitude during a standardized infusion of 15 ml Ringer over 10 min was useful in predicting response to shunt surgery and can be used as a screening procedure for selection of iNPH patients for shunting.

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Background

The clinical condition normal pressure hydrocephalus (NPH) incorporates gait disturbance, mental deterioration and urinary incontinence, combined with enlarged cerebral ventricles and a normal lumbar cerebrospinal fluid pressure (CSFP) [1]. Usually no cause is identified, in which case the condition is denoted idiopathic NPH (iNPH). Although the pathophysiology of iNPH is disputed [2], previous studies have shown that shunt surgery can be effective, and that clinical improvement can be sustained for years [3-5].

Hydrodynamic tests, in particular the lumbar infusion test, have been used for selecting patients for surgery, although the literature is very divergent concerning its role in iNPH [6]. During lumbar infusion testing, the static CSFP can either be monitored during constant flow infusion, constant pressure infusion or during bolus infusion to the thecal sac. In our practice, we have for many years used a modification of the constant rate infusion test originally described by Katzman [7] for determination of resistance to CSF outflow (R_{out}). However, the utility of R_{out} in selecting iNPH patients for surgery is controversial [8-13]. On the other hand, we have found that the ICP pulse (that is the amplitude of the single cardiac-beat induced ICP waves) during over-night ICP monitoring is very useful for predicting shunt response in iNPH [14]. Thus, in our previous series of 130 shunted iNPH patients, shunt response was seen in 9 of 10 patients with elevated ICP wave amplitudes but only in 1 of 10 with low ICP wave amplitudes [15].

With regard to lumbar infusion testing, the various approaches (e.g. constant flow, constant pressure or bolus infusion methods) consistently assess the static and not the pulsatile CSFP. Others [16] and our group [8,11,17] have reported experiences from assessing the pulsatile CSFP during lumbar infusion testing. Based on these experiences, it could be anticipated that determining the CSFP pulse during lumbar infusion testing might better characterize the pressure-volume reserve capacity than the static CSFP. Moreover, successful assessment of the pulsatile CSFP during lumbar puncture might represent an advantage, given that lumbar puncture is a low-risk procedure, and more useful in a clinical neurological setting than continuous ICP monitoring. The pulsatile CSFP can be measured during the opening phase of lumbar puncture, as well as during lumbar infusion. Thus, our goal with the present study was to establish a more reliable screening procedure for selection of iNPH patients for shunt surgery, based on determining the CSFP pulse amplitude during lumbar infusion testing. For this purpose, in the present study we explored how measurement of the pulsatile CSFP during lumbar infusion testing correlated with the ICP pulse monitored over-night and with the response to shunting. To do this we retrieved all lumbar infusion tests done during diagnostic work-up for iNPH in this department during the time period 2002-2007. These infusion tests were stored as continuous CSFP raw data (originally sampled at 100-200 Hz). In the present study, these raw data files were re-analyzed; the CSFP pulse amplitude was determined during the opening phase after lumbar puncture and also during a period of lumbar infusion (standardized as 15 ml infusion over 10 min). All patients had their ICP monitored over-night; therefore the infusion test results could be related to the pulsatile ICP recorded over-night, and with the clinical response to shunting.

Methods

Patient material

The patient material consisted of all patients being assessed for iNPH at the Department of Neurosurgery, Rikshospitalet University Hospital, during the 6-years period 2002-2007, in whom both over-night ICP monitoring and lumbar infusion testing had been done during the diagnostic pre-operative work-up. The patients were referred from local neurological departments based on their symptoms of gait disturbance, incontinence, and dementia, combined with radiological ventriculomegaly.

For diagnostic work-up the patients were hospitalized for 3 days. Following clinical and radiological assessment on day 1 (day of admittance), ICP monitoring was done from day 2 to day 3. The lumbar infusion test was done on day 3. After discharge from the department on day 3, they returned 1-3 weeks later for surgical treatment provided this was advocated.

This study was approved by the hospital authority of Rikshospitalet University Hospital and by the Norwegian Social Science Data Services. The Regional Committee for Research Ethics was informed in writing, and had no objections to the study.

Clinical and radiological assessment

Our diagnostic work-up for iNPH patients has previously been described [14,15]. In short, based on findings at neurological examination, the severity of clinical iNPH was graded using our NPH grading scale (scores ranging from 3-15), which assesses the combined severity of gait disturbance, urinary incontinence and dementia. The size of the ventricles was assessed using the linear measure Evan's index [14].

Diagnostic ICP monitoring and lumbar infusion testing

Diagnostic continuous ICP monitoring was done through a frontal burr hole prepared under local

anesthesia. A Codman ICP MicroSensor (Codman, Johnson & Johnson, Raynham, MA, USA) was placed 1-2 cm into the brain parenchyma. The ICP monitoring was done from the evening of day 2 until the morning of day 3. For each patient we used the over-night ICP recording from 11 p.m. to 7 a.m., when the patient was supine in bed.

On the morning day 3, the lumbar infusion test was done, as previously described [11]. Our strategy represents a modification of the original Katzman procedure [7]. The test was performed with the patient in the supine position by making a midline lumbar puncture with a 19-gauge needle between the L3 and L4 vertebrae (one puncture only). The lumbar cerebrospinal fluid (CSF) pressure was measured continuously using the Truwave PX-600F Pressure Monitoring Set (Edwards Life sciences LLC, Irvine, CA, USA), during the opening phase after lumbar puncture (P_o), and during infusion with a Ringer solution at a standard infusion rate of 1.5 ml/min (fig 1a). The resistance to CSF outflow (R_{out}) was calculated as the difference between the plateau pressure (P_p) and the opening pressure (P_o), divided by infusion rate [11,18].

Surgical treatment

The criteria for surgical treatment during this time period were based on a combination of clinical and radiological observations, and ICP monitoring, as previously described [15]. The infusion test was considered abnormal when resistance to CSF outflow (R_{out}) was ≥ 12 mmHg/ml/min. Surgical treatment was implantation of a ventriculo-peritoneal (VP) shunt: 46 patients received a HAKIM™ Programmable Valve Shunt System (Codman & Shurtleff, Inc. Medos S.A. CH 2400 Le Locle, Switzerland), and two patients received a programmable gravitational shunt (proGAV-Shunt system, Aesculap Miethke, Tutlingen, Germany.

Follow-up and outcome assessment

Follow-up was done in our out-patient clinic at regular time intervals, first at three months. As during the pre-operative examination, the NPH score expressed the combined severity of gait disturbance, urinary incontinence and dementia. If a patient at some time was unable to attend the clinic, he or she was interviewed by phone. The response to shunt surgery was determined after 12 months. We define an increase ≥ 2 scores on our NPH scale as representative of clinical improvement, a change which is generally appreciated by the patients and their families/proxies. Thus, the surgically treated patients were categorized either as Responders (change in NPH score ≥ 2) or Non-responders (change in NPH score < 2), respectively.

Analysis of pulsatile ICP and pulsatile lumbar CSF pressure

The continuous ICP/CSFP waveforms were stored on a hospital server (sampling rate 100-200 Hz). A method [14] implemented in software (Sensometrics software, dPCom As, Oslo) was used for retrospective analysis of the CSFP and ICP waveforms. In short, the automatic algorithm identifies the cardiac-beat induced single pressure waves within the continuous pressure signal. For each single pressure wave, pulsatility is characterized by the amplitude [pressure difference (dP) from systolic maximum to diastolic minimum; fig 1b]. For each consecutive six-second (6 s) time window (fig 1b, c), the method computes mean wave amplitude (representing the pulsatile pressure), and mean pressure (representing the static pressure). The 6 s parameter values can be plotted against time (fig 1a, d), and average values determined for selected time periods.

The pulsatile ICP was characterized as the average value of ICP wave amplitude over-night from 11 p.m. to 7 a.m. The pulsatile CSFP was determined both as the average of CSFP wave amplitude during the opening phase after lumbar puncture (fig 1d), and also as the average of CSFP wave amplitude during the standardized infusion time of 10 min, i.e. infusion of 15 ml during 10 min at a rate of 1.5 ml/min (fig 1d). We selected a standardized infusion period of 10 min (corresponding to a standardized infusion volume of 15 ml) to be able to compare all the infusion tests.

Statistics

Statistical analyses were performed in SPSS, version 12.0 (SPSS Inc., Chicago, IL, USA). Differences between groups were determined by one-way ANOVA. Correlations were calculated using bivariate analysis, with determination of Spearman correlations. Significance was accepted at the 0.05 level.

Results

Patients

During the period 2002-2007, a total of 214 iNPH patients underwent diagnostic ICP monitoring as part of pre-operative work-up in the Department of neurosurgery. A subgroup of 62 iNPH patients also underwent lumbar infusion testing the day following over-night ICP monitoring (Table 1). Median age of the total material was 72 years; their symptoms had lasted median 2.8 years (Table 1).

Results of diagnostic ICP monitoring and lumbar infusion testing

Diagnostic ICP monitoring caused minor complications in 4 of 62 patients (6.5%), which only included subcutaneous wound infections that were treated with

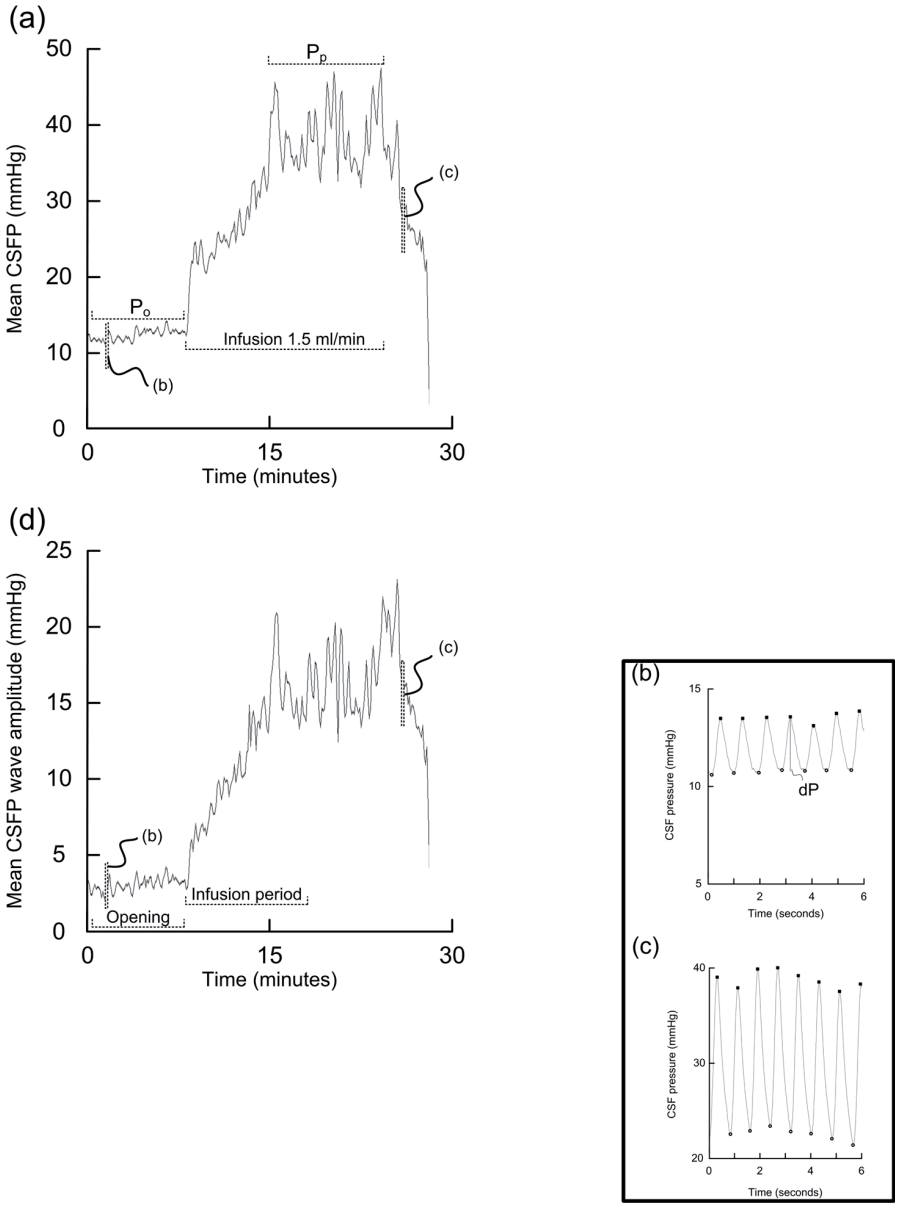

Figure 1 Analysis of lumbar infusion tests: (a) a plot showing our conventional method of performing a lumbar infusion test, using constant-rate infusion at 1.5 ml/min of Ringer solution. The plot of mean CSFP against time incorporates the period before infusion (opening pressure; P_o), and during the infusion period (infusion rate of 1.5 ml/min). The plateau pressure (P_p) is indicated. The resistance to CSF outflow (Rout) is calculated as (P_p - P_o)/infusion rate. Two 6 s time windows of the continuous CSFP signal from (b) the start and (c) the termination of the infusion test are indicated, illustrating the single CSFP pulse waves. (d) Plot of mean CSFP pulse amplitude against time, indicating the period after lumbar puncture and before infusion (opening phase), and the 10 min period during the infusion. For comparison between patients we compared the CSFP pulse amplitude during the first 10 min of infusion.

Table 1 Demographic data of the patient material

	All patients	Shunt Group	
		Non-Responders	Responders
Number	62	10	35
Age (yrs)	72 (37 - 85)	68 (47 - 81)	72 (47 - 81)
Sex (F/M)	31/31	5/5	18/17
Clinical state			
Duration of symptoms (yrs)	2.8 (0.3 - 10)	3 (1 - 10)	3 (1 - 8)
NPH score (15-3)	9 (4 - 14)	11 (6 - 14)	9 (4 - 13)
Radiology			
Evan's index	0.4 (0.3 - 0.5)	0.4 (0.3 - 0.5)	0.4 (0.3 - 0.5)

antibiotics without sequels. The lumbar infusion tests caused no complications.

The static ICP was normal in all patients (mean ICP 7.6 ± 4.8 mmHg). During over-night ICP monitoring (11 p.m. to 7 a.m.) the pulsatile ICP was elevated (i.e. mean ICP wave amplitude ≥ 4 mmHg) in 42 of 62 patients (68%; Table 2). The pulsatile CSFP was elevated in the sub-group with over-night pulsatile ICP (fig 2); this was seen during the opening phase after lumbar puncture (fig 2a), but was even more evident during the period of lumbar infusion (fig 2b). Thus, among 42 patients with elevated pulsatile ICP over-night (ICP wave amplitude ≥ 4 mmHg), the pulsatile CSFP was low (CSFP wave amplitude < 2 mmHg) in 17 subjects during the opening phase of lumbar puncture (fig 2a), while pulsatile CSFP was low (CSFP wave amplitude < 4 mmHg) in only 5 subjects during lumbar infusion (fig 2b). The numbers are further detailed in Table 2.

Clinical response to shunting related to the diagnostic ICP and infusion testing

Forty-five of the 62 patients were shunted, in whom 35 (78%) were shunt responders (Table 1). Major complications to shunt surgery were seen in 18% of patients (chronic subdural haematoma in 7%, shunt infection in 2%, visual failure in 2%, and shunt failure in 7%). Minor complications (headache, abdominal pain, dizziness) were seen in 13%.

Among the 45 patients being shunted, R_{out} ≥ 12 mmHg/ml/min was seen in 44 patients. Moreover, of these 44 patients, 35 (79.5%) were shunt responders, whereas nine (20.5%) were non-responders. There was a weak, though significant, correlation between R_{out} and change in NPH score (i.e. clinical improvement) 12 months after shunting (Spearman correlation 0.31; P = 0.04; one way ANOVA; data not shown).

When correlating the clinical improvement 12 months after shunting (change in NPH score) with the CSFP pulse, we found a highly significant correlation with the ICP pulse amplitude recorded over-night (Spearman correlation 0.58; $P < 0.001$; fig 3a). The clinical improvement after 12 months was not significantly correlated with the CSFP pulse measured during the opening phase after lumbar puncture (Spearman correlation, fig 3b). On the other hand, we found a significant correlation between the change in NPH score after 12 months and the CSFP pulse measured during lumbar infusion (15 ml over 10 min) (Spearman correlation 0.47; P = 0.002; fig 3c). These observations are further illustrated in fig 4. The shunt responders and non-responders were best differentiated by the over-night ICP monitoring (fig 4a), but were also differentiated by the CSFP pulse during the opening phase after lumbar puncture (fig 4b) and more so by the pulse during infusion (fig 4c).

The prediction of shunt response from results of ICP monitoring or lumbar infusion testing is presented in Table 3. The data show high positive predictive values (PPV) and negative predictive values (NPV) for ICP pulse amplitude recorded over-night, and also for the CSFP pulse during lumbar infusion.

Discussion

The main observation of this study is that the CSFP pulse amplitude determined during lumbar infusion testing showed good correlation with the ICP pulse amplitude recorded over-night, and also with the clinical response to shunting in iNPH. The data support our hypothesis that determining pulsatile CSFP during

Table 2 The CSFP pulse during lumbar puncture *versus* ICP pulse during over-night ICP monitoring

*Over-night ICP monitoring**	*Lumbar puncture*			
ICP wave amplitude	**CSFP wave amplitude during opening phase**		**CSF wave amplitude during lumbar infusion**	
	< 2 mmHg	≥ 2 mmHg	< 4 mmHg	≥ 4 mmHg
< 4 mmHg (n = 20)	17	3	12	8
≥ 4 mmHg (n = 42)	17	25	5	37
Statistics	Sensitivity = 60; Specificity = 85 PPV = 89; NPV = 50		Sensitivity = 88; Specificity = 60 PPV = 82; NPV = 71	

*Mean ICP wave amplitude from the period 11 p.m. to 7 a.m.

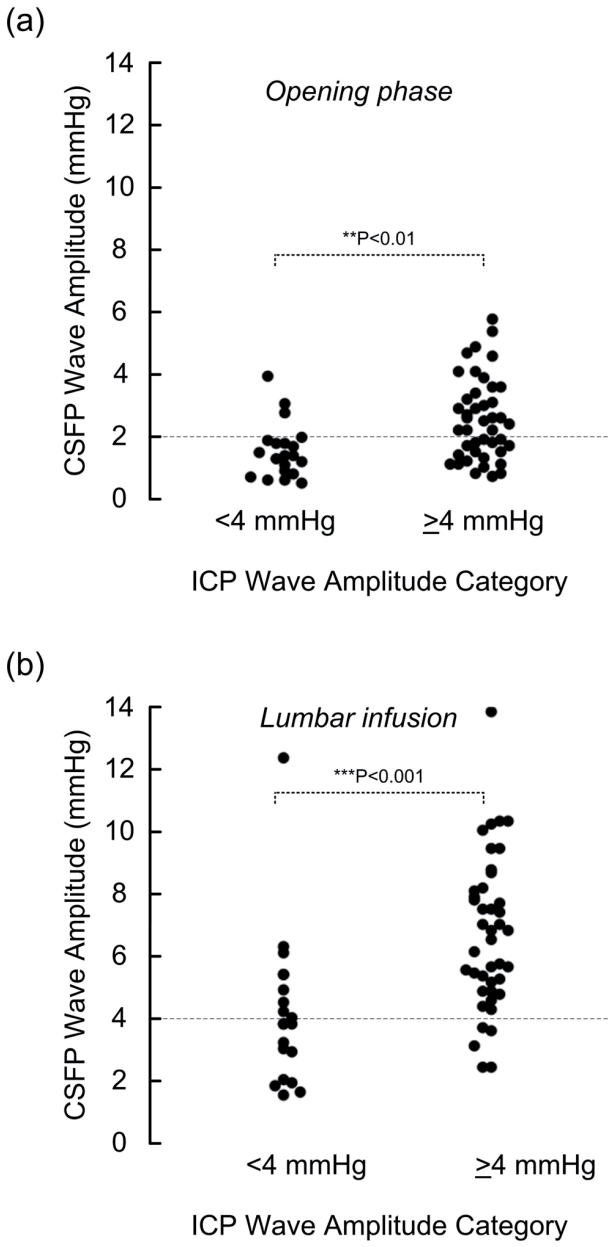

Figure 2 Scatter plots of CSFP wave amplitude during the opening period and during lumbar infusion for the two categories of overnight pulsatile ICP (mean ICP wave amplitude either < 4 mmHg or ≥ 4 mmHg during the period 11 p.m. to 7 a.m.) a) Shows the pulsatile CSFP (mean CSFP wave amplitude) during the opening phase after lumbar puncture, and (b) during the phase of lumbar infusion (15 ml over 10 min; 1.5 ml/min). Dotted lines denote different targets for CSFP wave amplitude during the opening period and during lumbar infusion. Significant differences between groups were tested with one-way ANOVA.

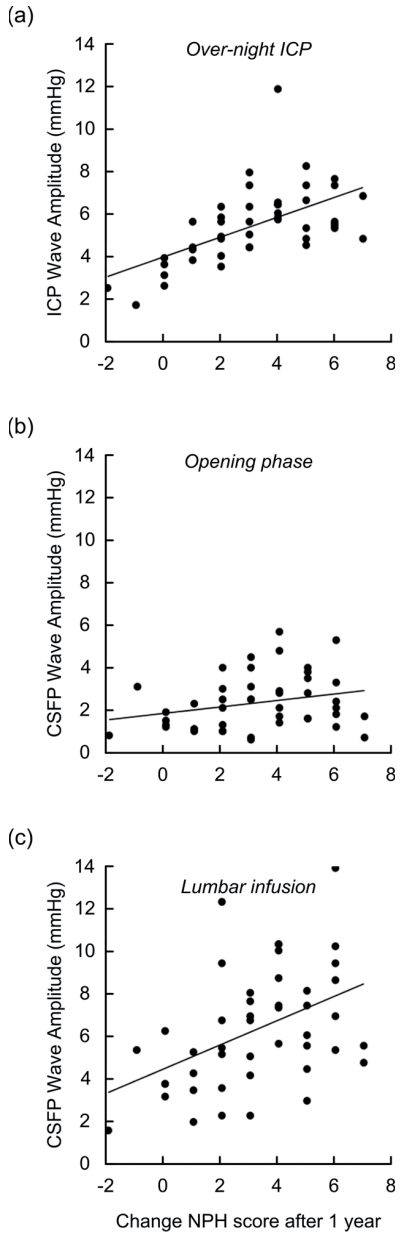

Figure 3 Graphs showing the correlation between changes in NPH Score one year after shunt surgery and (a) ICP wave amplitude during over-night ICP monitoring, (b) CSFP wave amplitude during the opening phase after lumbar puncture, and (c) CSFP wave amplitude during the phase of lumbar infusion (15 ml over 10 min; 1.5 ml/min).

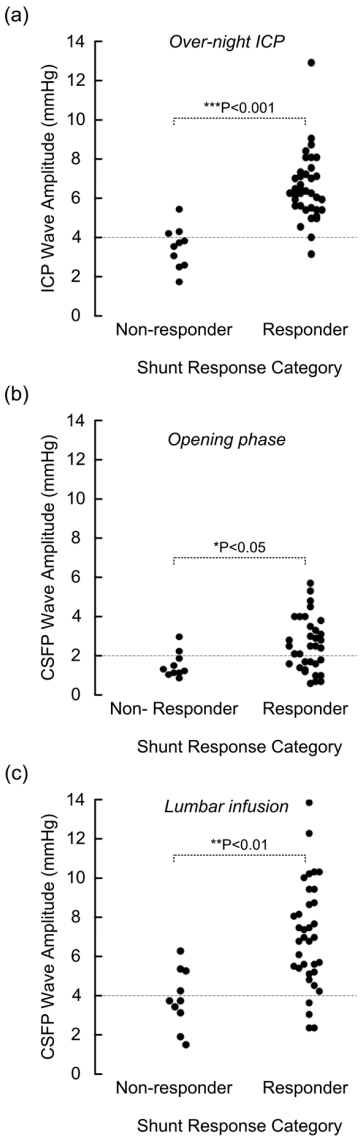

Figure 4 Scatter plots of mean CSFP wave amplitude for shunt response categories non-responder and responder during (a) over-night ICP monitoring, (b) during the opening phase after lumbar puncture, and (c) during the phase of lumbar infusion. Dotted lines denote cut off targets for the pulsatile pressure (wave amplitude). The pulse amplitude during the opening phase of lumbar puncture was not as good a predictor for shunt response as the amplitude during overnight monitoring and during lumbar infusion. Significant differences between responders and non-responders are shown (one-way ANOVA).

Table 3 Number of shunt responders/non-responders depending on results of lumbar puncture or ICP monitoring

	Lumbar puncture				*ICP monitoring**	
	CSFP wave amplitude during opening phase		**CSF wave amplitude during lumbar infusion**		**ICP wave amplitude**	
	< 2 mmHg	≥ 2 mmHg	< 4 mmHg	≥ 4 mmHg	< 4 mmHg	≥ 4 mmHg
Responder (n = 35)	13	22	4	31	1	34
Non-Responder (n = 10)	8	2	6	4	7	3
Statistics	Sensitivity = 63; Specificity = 80 PPV = 92; NPV = 38		Sensitivity = 88; Specificity = 60 PPV = 89; NPV = 60		Sensitivity = 97; Specificity = 70 PPV = 92; NPV = 88	

* Mean ICP wave amplitude from the period 11 p.m. to 7 a.m. PPV = Positive predictive value; NPV = Negative predictive value.

lumbar infusion can be useful as a screening procedure for selection of iNPH patients for shunting.

Patients

We have previously reported our entire experience of managing iNPH patients using diagnostic ICP monitoring in the pre-operative work-up during the period 2002-2007 [15]. The present subgroup of 62 iNPH patients managed during the same time period represented the patients that also underwent lumbar infusion testing on day 3. The reason for doing lumbar infusion testing in these patients was that lumbar infusion testing has been done since the 1980's in this department, and thus represented the traditional management. Therefore, we considered how this subgroup compared with our entire cohort of iNPH patients. The present group of 62 patients compared well with our entire cohort during this time period regarding age, sex, symptom duration, severity of symptoms and ventricular size (Table 1) [15]. Moreover, in our entire cohort of 130 shunted iNPH patients, 79% were shunt responders [15], as compared to 78% of 45 shunted iNPH patients in the present study. The present material is therefore representative of our entire experience of managing iNPH. In comparison, McGirth *et al*. [4], using 3-days external lumbar drainage (ELD) and positive finding of A- or B-waves on spinal puncture, found in 132 patients a long term shunt response rate of 75%. Moreover, using gait improvement after 3-days ELD to aid selection for surgery, Marmarou *et al*. [3] reported clinical improvement in 76 (91%) of 84 patients.

Overnight pulsatile ICP versus pulsatile CSFP during lumbar infusion testing

Based on our experience of diagnostic ICP monitoring in 214 iNPH patients [15], we categorized pulsatile ICP as being elevated when ICP wave amplitude is ≥ 4 mmHg during over-night monitoring. Thus, among 130 shunted iNPH patients, 93% with elevated ICP pulse (i.e. ICP wave amplitude ≥ 4 mmHg during over-night monitoring) were shunt responders whereas only 10% with low ICP pulse (i.e. ICP wave amplitude < 4 mmHg over-night) responded to shunting [15]. In the present group, 68% of patients had elevated ICP pulse.

The present dataset clearly showed that pulsatile CSFP was elevated in those with elevated over-night ICP pulse. This was most evident during the period of lumbar infusion, as compared to the opening phase after lumbar puncture (fig 2; Table 2). Examining simultaneous measurements of lumbar CSFP pulse and intracranial ICP pulse during lumbar infusion testing, we have previously shown in 35,532 CSFP/ICP single wave pairs that the lumbar CSFP wave amplitudes are about 2 mmHg below the simultaneous cranial ICP wave amplitudes [17]. Thus, from this experience, we categorized ICP wave amplitudes ≥ 4 mmHg as indicative of elevated pulsatile ICP [15], and lumbar CSFP wave amplitude ≥ 2 mmHg as indicative of elevated pulsatile CSFP [8,17].

One explanation for this discrepancy between the intracranial and intraspinal compartments is the difference in compliance (i.e. pressure-volume reserve capacity) between the compartments. This assumption is further illustrated in fig 5; the pressure-volume curve of the intraspinal compartment is moved to the right as compared to the curve of the intracranial compartment, indicative of higher compliance in the intraspinal than the intracranial compartment. A methodological drawback relates to the fact that the pulsatile CSFP during lumbar infusion testing was measured through the same needle as the infusion. Therefore the pulsatile CSFP during infusion might be slightly increased due to the resistance of the lumbar needle at the infusion rate of 1.5 ml/min. Measurements from a second needle might prevent this effect, and give slightly lower pulsatile CSFP values. However, the impact of this effect is probably minor. Thus, simultaneous measurements of pulsatile ICP and lumbar pulsatile CSFP during lumbar infusion showed that the lumbar CSFP pulse amplitudes were about 2 mmHg below the ICP pulse amplitudes both before and during the infusion [17].

In the present study, we solely focused on the pulsatile pressures. In line with our previous experience [15], over-night static ICP was normal in these patients

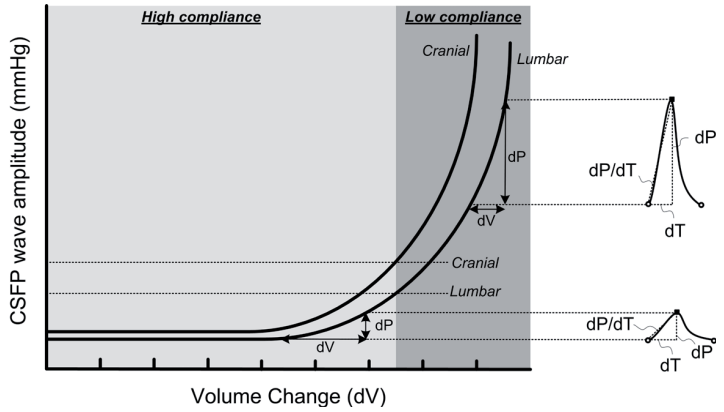

Figure 5 Assessments of intracranial compliance and lumbar compliance during lumbar infusion. This diagram illustrates the intracranial and lumbar pressure-volume curves and the relationship to the pulsatility parameters. Under normal physiologic conditions with high intracranial compliance, ICP wave amplitude is correspondingly small. As intracranial compliance decreases (steep part of the pressure-volume curve), the brain behaves increasingly like a linear elastance and so variations in intracranial volume correlate increasingly well with changes in ICP wave amplitude, thus the steepness of the pressure-volume curve accounts for large-amplitude ICP waveforms. The cranial pressure-volume curve is left of the lumbar pressure-volume curve, illustrating that compliance is higher in the lumbar compartment.

(hence the term normal pressure hydrocephalus). Others have previously examined differences in the static pressures between intraspinal and intracranial compartments. Several authors have found that the short-lasting opening CSFP measured during the opening phase of lumbar puncture (opening pressure) did not relate well to ICP recorded over-night [17,19,20]. Others found lumbar mean CSFP to agree with the ICP across a large pressure interval [21]. The reason for the discrepancy is that the static pressure depends on the baseline level and zero calibration since the static pressure refers to the difference between the atmospheric pressure and the intra-compartment pressure [22,23]. The pulsatile pressure, characterized by the wave amplitude, on the other hand, refers to the intra-signal difference between the diastolic and systolic pressures (fig 1), thus being independent of the baseline pressure level [22,23]. We have previously shown that the two sensors used for pressure monitoring in this study are equivalent for pulse pressure wave analysis; comparing a total of 218,589 single pressure wave pairs from the intracranial compartment from these two pressure sensors revealed a difference in pulse pressure amplitude of only 0.13 mmHg (95% confidence interval 0.12 -0.13 mmHg) [23].

Clinical response to shunting related to the diagnostic ICP and infusion testing

Among those 37 patients with elevated ICP pulse overnight (i.e. mean ICP wave amplitude ≥ 4 mmHg; time period 11 p.m. - 7 a.m.), 34 (92%) were shunt responders, while among those eight with low ICP pulse overnight (i.e. mean ICP wave amplitude > 4 mmHg; time period 11 p.m. - 7 a.m.) only one (13%) responded to shunting (Table 3). These numbers compare with our entire series of shunted iNPH patients during this same time period (2002-2007) [15].

During lumbar infusion testing, our standard approach has been to determine resistance to CSF outflow (R_{out}). The cut-off value for considering R_{out} pathologically elevated varies in the literature. According to our routine, we have considered R_{out} ≥ 12 mmHg/ml/min as abnormal [6,12]. Therefore, among our 45 shunted iNPH patients, R_{out} ≥ 12 mmHg/ml/min was seen in all but one patient. Among the resulting 44 patients, 35 (80%) were shunt responders. In general, the role of R_{out} in predicting shunt response is still highly disputed [6,8-10,13]. Based on our earlier experience with determination of R_{out} [8,11], we have now discontinued using the R_{out} for the purpose of selecting iNPH patients for shunting.

In this cohort, we found a highly significant correlation between overnight pulsatile ICP and the degree of clinical improvement seen 12 months after shunting (fig 3a). The correlation between R_{out} and clinical improvement was weaker, though it reached significance. These observations compare with our previous experience [8,11,15]. A new observation here was that the CSFP pulse amplitude measured during lumbar infusion (15 ml over 10 min) correlated better with clinical improvement after shunting (fig 3c). This latter observation

compares with recently reported observations, focusing on the distribution of the CSFP pulse during lumbar infusion testing [8]. It should be noted that prior to shunting the R_{out} and not the CSFP pulse was used to select patients for shunt surgery. As shown in Table 3, clinical response to shunting was best predicted by over-night ICP monitoring, in line with previous observations [15]. The most important observation of this study is that clinical shunt response was also predicted by the CSFP pulse during lumbar infusion (Table 3). Thus, when CSFP wave amplitude was ≥ 4 mmHg during lumbar infusion of 15 ml over 10 min, clinical response to shunting was predicted with a sensitivity of 88 and specificity of 60 (PPV 89; NPV 60).

Taken together, the present results suggest that determining CSFP pulse amplitude during lumbar infusion testing can be useful as a screening procedure for selection of patients to shunt surgery. An advantage of lumbar infusion testing, as compared to over-night ICP monitoring, is that the procedure is a low cost and low threshold approach with few complications that is widely used. Moreover, determining the CSFP pulse was more useful than the R_{out} determination.

Measuring pulsatile CSFP during lumbar infusion versus intracranial compliance

Figure 5 provides a tentative explanation of what is being tested while monitoring pulsatile CSFP during lumbar infusion. We assume that the CSFP pulse provides an indirect measure of the compliance (pressure-volume reserve capacity) of the intraspinal compartment. When the compliance is being reduced, the amplitudes (dP) are increasing [24,25]. The wave amplitude (dP) is the pressure response to the volume change caused by each cardiac contraction, which in the intracranial compartment is about 1 ml [26]. During lumbar infusion the compliance is being artificially reduced (moving to the right on the pressure-volume curve). When compared to the cranial pressure-volume curve, the spinal pressure-volume curve is shifted to the right because compliance in the spinal compartment is higher than in the intracranial compartment [17]. For this reason it is necessary to infuse fluid intrathecally to reach the same amplitude values in the lumbar compartment as in the intracranial compartment. Although the wave amplitudes do not measure compliance directly, they are related to compliance [27] and elevated ICP pulse is associated with reduced intracranial compliance [28]. An important effect of shunting is improved compliance and this is why elevated ICP pulse measured during over-night ICP monitoring and also during lumbar infusion, accurately predicts the shunt response in these patients (Table 3).

Conclusions

Taken together, determining CSFP pulse amplitude during lumbar infusion in this cohort of iNPH patients was useful for predicting shunt response. The data suggest that the approach can be used for screening of iNPH patients for shunt surgery.

List of abbreviations

CSFP: Cerebrospinal fluid pressure; dP: Single wave amplitude; ELD: External lumbar drainage; ICP: Intracranial pressure; iNPH: Idiopathic normal pressure hydrocephalus; NPV: Negative predictive value; P_o: Opening pressure; P_p: Plateau pressure; PPV: Positive predictive value; R_{out}: Resistance to cerebrospinal fluid outflow.

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Authors' contributions
The authors contributed equally to this work. Both authors have read and approved the final manuscript.

Competing interests
Dr Eide has a financial interest in the software company (dPCom AS, Oslo) which manufactures software licensed to the Department of Neurosurgery, Oslo University Hospital - Rikshospitalet, and used for analysis of the ICP recordings (Sensometrics Software). Dr. Brean reports no competing financial or non-financial interests.

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