Predicting the response to ventriculoperitoneal shunt in patients with Normal Pressure Hydrocephalus

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Declaration

All work contained within this thesis has been performed by myself unless otherwise specified. On occasions Mr Imran Bhatti, registrar in neurosurgery, reviewed some patients at the Royal Preston hospital for any acute problems and shunt pressure adjustments. Physiotherapists in the neurosurgery department performed the gait assessments and specific protocol was adhered.

Abstract

Objective:

The diagnosis and management of normal pressure hydrocephalus (NPH) remains controversial. The aim of this prospective study was to assess the usefulness of clinical and radiological criteria together with supplemental neuropsychological and gait tests, cerebrospinal fluid (CSF) hydrodynamic studies and external lumbar drainage (ELD) in identifying those who may respond to a shunt and to compare the outcomes with the non-shunted patients at one year.

Method:

Forty patients with a clinical diagnosis of NPH were prospectively studied according to a fixed management protocol. Resistance to CSF (Rcsf) was measured using a lumbar infusion study and an ELD was used to determine improvement in neuropsychological and gait tests following CSF drainage. Based on specific criteria those who showed improvement were shunted. Clinical and radiological outcomes were assessed at one year in all patients.

Results:

Twenty three (57.5%) patients were shunted. Improvement was observed in 74% of shunted patients, while 17% did not improve and 9% deteriorated following surgery. Age, etiology, presentation, duration of symptoms and presence of co-morbid factors were unrelated to outcome. Improvement was found in 63% of shunted patients with RCSF of 12 mmHg/ml/min or higher. The sensitivity was 64% with a positive predictive value of 68%. Both Rcsf testing and ELD enhanced the positive predictive outcome of shunt operation. Using the non-shunted

patients as controls, the mean difference between the two groups over time differed significantly in all the neuropsychological tests and some gait test.

***Conclusions*:**

No single test was able to predict overall success with shunting but the results showed that a high percentage of improvement could be achieved by using continuous ELD and a rigorous protocol. Greater improvements were observed in cognitive and gait function than in sphincter control. An Rcsf of 12mmHg/ml/min or more was related to better outcomes. Consideration was given to the significant limitations in the study design and outcome measures.

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Abbreviations

AD	-	Alzheimer's disease
ATP	-	Adenosine triphosphate
AVM	-	Arterio-venous malformation
BDI	-	Beck depression index
CANTAB	-	Cambridge neuropsychological test automated battery
CBF	-	Cerebral blood flow
CCH	–	Chronic communicating hydrocephalus
Cho	-	Choline
CO_2	-	Carbon dioxide
Cr	-	Creatine
CRF	-	Corticotrophin releasing factor
CSF	-	Cerebrospinal fluid
CT	-	Computerised tomography
CVD	-	Cerebrovascular disease
EI	-	Evans' index
ETV	-	Endoscopic third ventriculostomy
ELD	-	External lumbar drain
FHI	-	Frontal horn index
GFAP	-	Glial fibrillary acid protien
HI	-	Head injury
IHD	-	Ischemic heart disease
Hg	-	Mercury

ICP	-	Intra cranial pressure
ID/ED	-	Intra dimensional / Extra dimensional
IQ	-	Intelligent quotient
LP	-	Lumbar puncture
LPS	-	Lumbo-peritoneal shunt
NAA	-	N-acetyl aspartate
NART	-	National adult reading test
NFL	-	Neurofilament triple protien
NPY	-	Neuropeptide Y
NPH	-	Normal pressure hydrocephalus
MMSE	-	Mini mental state examination
MRI	-	Magnetic resonance imaging
PET	-	Positron emission tomography
PD	-	Parkinson's disease
PHFs	-	Peri-hippocampal fissures
PCr	-	Phosphocreatine
Pi	-	Inorganic phosphate
iNPH	-	Idiopathic normal pressure hydrocephalus
SAH	-	Subarachnoid haemorrhage
SAE	-	Sub cortical arteriosclerotic encephalopathy
sNPH	-	Secondary normal pressure hydrocephalus
SOM	-	Somatostatin
SPECT	-	Single photon emission computed tomography

Rout	-	Resistance to outflow
Rcsf	-	Resistance to cerebrospinal fluid
rCBF	-	Regional cerebral blood flow
rCBV	-	Relative cerebral blood volume
TT	-	Tap test
VF	-	Verbal fluency
VPS	-	Ventriculo-peritoneal shunt
VAS	-	Ventriculo-atrial shunt
WMH	-	White matter hyper intensities

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Dedication

To my parents Visalakshi and Gopalakrishnan for their everlasting love and tireless support provided during all endeavours in my life. To all my teachers who have been an inspiration to persevere my interests in Neurosurgery and research.

Inspired quotes

There is more to life than simply increasing its speed.

We must be the change we wish to see.

- Mahatma Gandhi

An idea that is developed and put into action is more important than an idea that exists only as an idea.

Thousands of candles can be lighted from a single candle, and the life of the candle will not be shortened. Happiness never decreases by being shared.

- Gautama Buddha

Work is an expression of who you are. So who you are is what needs to be worked out.

- Sadhguru Jaggi Vasudev

Presentations

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Media publication

Balamurali G. Link: “the magazine for people with hydrocephalus and spina bifida” *Issue 209, summer 2004. Page 23. – NPH research Hope.*

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Chapter 1: Introduction

1.1. Introduction

There are few dilemmas for the clinician in the management of acute non-communicating hydrocephalus, in which the urgent need to bypass an obstruction to cerebrospinal fluid (CSF) flow, is self-evident. The core pathophysiological process is the elevation of intracranial pressure above cerebral perfusion pressure and consequent tissue hypoxia and ischemia. The diagnosis is usually clear from the clinical features. There is usually a preceding history, which includes headache and an evolution through nausea, and vomiting, confusion and coma in association with appropriate clinical signs on examination. In addition there are confirmatory investigation results, which usually include sophisticated neuroimaging techniques. Chronic communicating hydrocephalus (CCH), in stark contrast, challenges the clinician with both diagnostic and management dilemmas. This is primarily because the diseases processes underlying these conditions are poorly understood but they probably also involve an interaction between tissue perfusion and intracranial pressure. In addition, the onset of these conditions is insidious; the differential diagnosis is wider than for acute onset hydrocephalus and the results of surgical intervention are unpredictable leading to a spectrum of outcomes ranging from possible significant recovery to potentially hazardous complications.

Normal pressure hydrocephalus is a syndrome of gait disturbance, dementia and urinary symptoms in the presence of ventricular enlargement and normal intracranial pressure. Hakim and Adams first described this condition in 1965. It can occur in people of any age, but it is most common in the elderly population above the age of 65 years. NPH is rare, estimated to account for 0.4% of cases of dementia (Vanneste, 1994). The likelihood is that it represents the final

common pathway of a number of different pathologies and symptoms are likely to be due to a combination of mechanisms rather than a single cause. Half of the cases are idiopathic (iNPH) and half are secondary NPH (sNPH) cases following head injury (HI), subarachnoid haemorrhage (SAH), meningitis or neurosurgery (Vanneste, 1994. Ojemann, Fisher, Adams et al, 1969).

Idiopathic normal pressure hydrocephalus (iNPH) accounts for a significant proportion of cases of CCH. It is already recognised as an important cause of cognitive impairment because it has for decades been thought to be reversible by surgical means. As our population continues to age, the social and economic importance of this condition is likely to grow and yet there are no reliable clinical or neuroimaging criteria to distinguish it from other chronic encephalopathies such as diffuse small vessel cerebrovascular disease, which can have very similar clinical and imaging features. Amongst the many causes of cognitive and motor dysfunction in the elderly, NPH is almost unique in that ventriculo-peritoneal shunting may result in marked recovery. This procedure involves diversion of CSF from the ventricles into the peritoneal cavity via shunt tubing. Shunting, particularly in elderly patients, is associated with a significant incidence of both acute and cumulative longer-term complication. Not all subjects respond to shunting, however, an acute complication rates of between 30-40% with rates of serious complications occurring at about 5-8% have been quoted following surgery (Vanneste, Augustijn, Dirven et al, 1992).

In CCH the decision to insert a ventriculo-peritoneal shunt which may be in situ for years and can arrest the disease process or even result in dramatic recovery, has to be balanced against the risk of acute and chronic complications some of which are life threatening. There are no robust criteria to predict outcome from this surgery in patients with NPH and even the decision to operate in the non-NPH CCH can be difficult because patients rarely present with raised

intracranial pressure (ICP) (Kirkpatrick, Engleman, Minns, 1989) and ventricular size does not correlate with ICP (Hanlo, Gooskens, van Schooneveld et al, 1997. van der Knaap, Valk, Bakker et al, 1991). The concern about these complication rates associated with an otherwise curative treatment of cognitive and gait decline has contributed to the drive to investigate the underlying processes in this disease. This is required to develop reliable non-invasive techniques to measure disease activity, which can then be used to guide management decisions such as whether, and when to operate. The bulk of the literature on this condition has been aimed at the development of reliable techniques for predicting outcome from surgery in order to better target this invasive form of therapy. In this systematic prospective clinical study we have tried to identify some reliable factors that can be used to predict those who are most likely to respond to a shunt than the others suspected to have a similar presentation.

1.2. History of Normal Pressure Hydrocephalus

The term "Normal Pressure Hydrocephalus" was introduced by Solomon Hakim in his thesis *Some Observations on CSF Pressure: Hydrocephalic syndrome in Adults with "Normal" CSF Pressure* in March 1964, Colombia. Adams and colleagues published the first article in the New England Journal of Medicine in 1965. During the same year Hakim and Adams in the Journal of Neurological Science (Hakim and Adams 1965) described the *"Classical triad"* of gait disturbance, incontinence and dementia characterized by normal opening pressures at lumbar puncture (LP) and improved on removal of CSF. He discussed three cases, two posttraumatic and one idiopathic hydrocephalus. In the last four decades since it was first described considerable controversy has evolved as to the appropriate diagnosis, investigation and management of the NPH patients. There are more than 1850 papers in the English literature between 1965 and 2008 that have looked into this condition. Of these, several studies have focused on identifying those

who will respond to a shunt surgery. Despite the advances and a slightly better knowledge of the disease the postoperative results of shunt implantation has not improved significantly. Only a few studies report an extended follow-up of patients and the value of the predicting factors in the long term.

1.3. Clinical features

A review of the clinical features of NPH may be helpful in determining the site and nature of the pathophysiology. Idiopathic form of NPH tends to present in the elderly above 65 years whereas patients with secondary form of NPH tend to present at an earlier age.

The original concept of Hakim and Adam's triad of symptoms (Hakim and Adams, 1965), namely impaired consciousness and reduced responsiveness in combination with locomotor and sphincteric difficulties in two patients with secondary and one patient with iNPH has evolved. At one stage the cardinal features were dementia, "apraxic" gait (Sudarsky and Ronthal, 1983) and urinary incontinence but even this has been refined further.

When six patients (4 with iNPH) were subjected to detailed neurological examination and gait analysis (Estanol, 1981) the gait impairment was found to be part of a subtle constellation of motor deficits, including failure of postural righting reflexes, a feature commonly seen in diseases of the basal ganglia such as Parkinson's disease. Interestingly, the term "apraxic" has been used to describe the gait. The problem, however, may not be just in the programming of the movement where the individual elements are adequately performed but not put together to complete the task. Rather the gait difficulty may be manifest only when weight is put on the legs. It has been suggested that this is due to release of positive proprioceptive supporting reactions or put another way a defect of supraspinal modulation of locomotion (Estanol, 1981). Interestingly

none of the patients studied had signs of idiomatic or ideational apraxia or agnosia. Grasp, snout and sucking reflexes are observed which are commonly seen with diffuse frontal lesions. Abnormal smooth pursuit, a feature of occipital disease and failed suppression of vestibulo-ocular reflexes seen in brainstem disease are also observed (Estanol, 1981). Difficulties with gait are an early feature, and have been described variously as, "shuffling" (Estanol, 1981), "magnetic" gait, "ignition failure", "bradykinetic", "glue-footed", "short-stepped", "apractic", and "lower body Parkinsonism" all of which are more in keeping with a disorder of higher order regulation of gait rather than a simple disorder of the pyramidal system. Gait is characterised by perseveration of posture (a frontal lobe feature), wide base, and slow, small steps with reduced range of foot-floor clearance. The presence of increased tone with brisk tendon reflexes in the lower limb and the absence of weakness or in-coordination (Estanol, 1981), suggest disruption of accessory circuits involved in the higher order production of gait. The plantar responses may be flexor or extensor, unilaterally or bilaterally. An early hypothesis suggesting that enlarged ventricles in NPH led to the compression and deformation of upper motor neuron fibers, passing through the corona radiate, is not supported by a recent study using motor evoked responses (Bech-Azeddine, Walder, Knudsen et al, 2001). Electromyographic evidence reveals contraction of antagonistic muscles and abnormally increased activity in the antigravity muscles acting on hips and knee joints (Bench, Waldemar, Gjerris et al, 1999, Boon, Tans, Delwel et al, 1997). This disturbance in the phased activation of muscle groups suggests a subcortical motor control problem and clearly suggests that pyramidal tracts are not necessarily involved in the disease process. Fisher, 1982 noted that hand tremor; writing disturbances and fine motor activity can also be affected in NPH. Impaired input from the sensorimotor cortex, the superior frontal cortex, and the anterior cingulate gyrus to the reticular formation in the tegmentum of the brain stem may

also contribute to the gait and stance disorder (Nutt, Marsden and Thompson 1993). Gait is known to be the earliest symptom noticed by the patient followed by cognitive and urinary symptoms and the first one to resolve following successful VP shunting (Graff-Radford and Godersky, 1987). Patients who have a lesser duration of symptoms are known to have a better outcome with shunting.

Boon, Tans, Delwel et al, 1997, in the Dutch normal pressure hydrocephalus study proposed that sub cortical dementia is mild to moderate. These patients had memory deficits, diminished visuospatial abilities, inertia, and psychomotor slowing. Similarly to Thomsen, Borgesen, Bruhn et al, 1986, patients were classified into groups according to their scores on the psychometric tests. An analysis of the duration of the illness found no relationship between length and the severity of NPH. The symptom duration ranged from 4 months up to 10 years. Twelve of those were diagnosed with NPH due to neurological conditions whereas the remaining 89 were idiopathic. The results, supporting previous findings, found that the dementia caused by NPH varied from mild cognitive problems through to severe impairment and an inability to even complete psychometric tests. In contrast to previous findings, this study indicated that length of illness did not correlate with extent of dementia, although reasons for this are unclear. It suggests however, that the dementia in NPH is not progressive. Meier, Zeilinger, and Kintzel, 1996, found higher rates of improvement following shunt surgery, of 65% at short term follow up. A mild regression was noted at long term follow up as only 54% remained improved (Thomas, McGirt, Woodworth et al, 2005).

In the initial stages incontinence may be due to gait disturbances when the patient cannot physically get to the toilet within the necessary time. In the more advanced stage the urinary

features are initially of urgency and later frank disinhibition suggestive of a frontal lobe element to the disease (Vanneste, 2000). It is suggested that the bladder disturbance is due to the distending of the periventricular nerve fibres and ensuing (partial) 'loss of inhibition of bladder contractions', (Vanneste, 2000). This impairment in bladder control often results in the patient feeling a strong, immediate sensation of a need to urinate (every one to two hours). In some cases there is a complete loss of bladder control, and although rare, cases of double incontinence have been reported. Bowel incontinence is usually present in more advanced stage. Some patients however never develop bladder dysfunction. Meier, Zeilinger and Kintzel, 1999 found urinary incontinence to be present in 24% of those in the early stages of NPH and 54% of those in the late stages. This supports previous findings that incontinence is not always a predominant symptom. The bladder `hyperactivity' can be temporarily alleviated by removal of 50mls of CSF through a lumbar drain and shunt insertion improves incontinence problems in this group of patients. Ahlberg, Norlen, Blomstrand et al, 1988 noted this improvement in all NPH patients following CSF drainage, but not in those with Alzheimer's disease or multi-infarct dementia. They suggest that urodynamic testing may be of benefit in differentiating between NPH and other causes of incontinence.

The characteristic which links these features is that these symptoms can be localised predominantly to the sub cortical white matter, the brain tissue in close proximity to the ventricles and this suggests that investigation of the cortex is unlikely to be fruitful and that investigation should be directed at the periventricular tissues.

1.4. Radiological diagnosis

1.4.1. Introduction

As mentioned previously the diagnosis of NPH is based on clinical symptoms and radiological confirmation of communicating hydrocephalus. Radiological confirmation is either by computed Tomography (CT) scan and or Magnetic Resonance Imaging (MRI) scan. The prognostic value of CT and MRI on their own is limited and other supplementary tests are necessary to increase the prognostic accuracy of identifying NPH responders to shunting.

1.4.2. Computerised tomography techniques (C.T)

CT scan not only helps in diagnosis along with the clinical symptoms, but it also helps to differentiate from other conditions that may mimic NPH (Table 1.1). In the normal population the mean ventricular size, as a percentage of the intracranial area, was 5.2% between ages 50-59, 6.4% from age 60-69, 11.4% from 70-79 and increased further to 14.1% between ages 80-89 years (Barron, 1976) These normal ventricular enlargements need to be noted when analysing CT scans in these patients. In NPH there is no significant cerebral atrophy compared to others causes of dementia. It is important to differentiate the ventriculomegaly of NPH from the 'hydrocephalus *ex vacuo*' of advanced Alzheimer's disease. Peri-hippocampal fissures (PHFs) are normal or only minimally dilated in NPH, and typically markedly dilated in Alzheimer's disease. Figure 1.1 shows a CT scan of a patient with NPH.

Figure 1.1: CT scan slices of a patient with NPH.

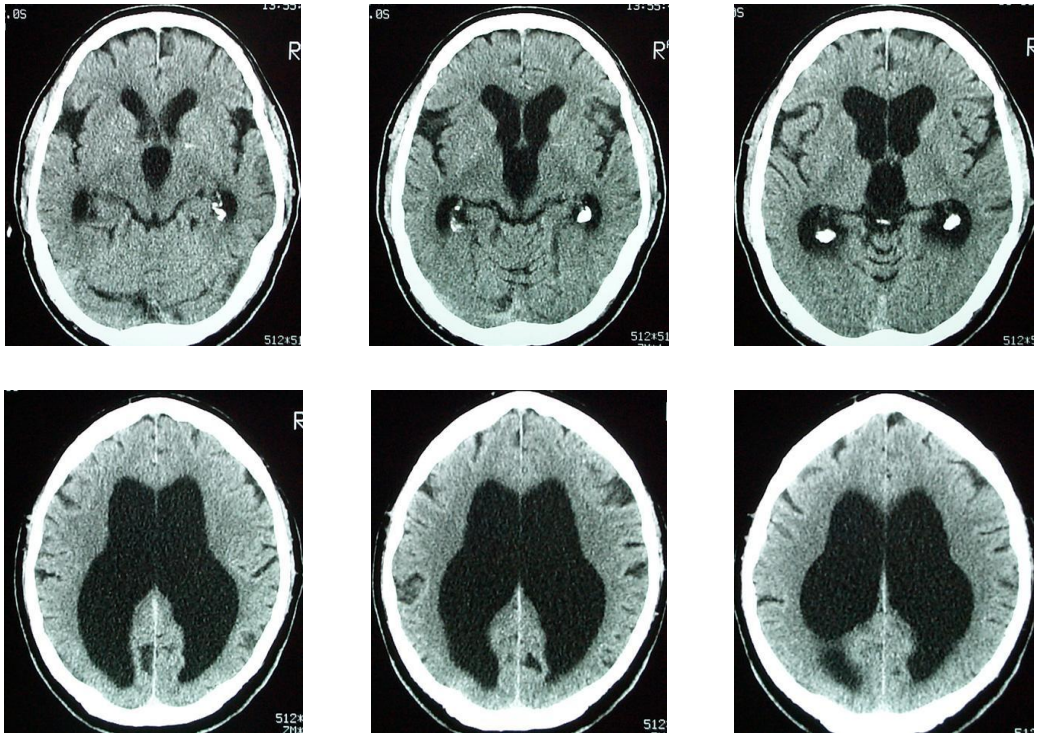
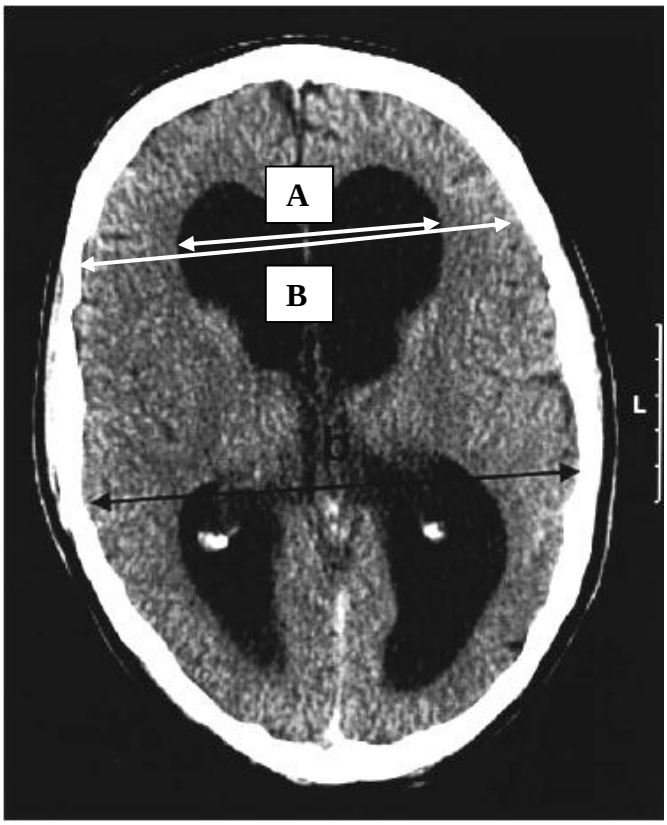


Figure 1.2: CT scan showing the calculation of Evans' index



Evans' index = A / B

The Evans' Index (EI) or Frontal Horn Index (FHI), which is determined by the largest diameter of the frontal horns divided by the diameter of the internal skull at the level of the frontal horns, if above 0.3 indicates ventriculomegaly, may possibly be the only finding obligatory for establishing the diagnosis of NPH (Figure 1.2). All the other imaging findings, i.e. large temporal horns, dilated third ventricle, enlarged peri-sylvian fissures or both focal dilation and obliteration of cortical sulci, cortical and subcortial atrophy and the "so-called" periventricular oedema have never been consistently reported in larger patient's series (Mori, Handa, Murata, et al., 1980, Wikkelso, Andersson, Blomstrand et al., 1989). Frontal Horn Index

(FHI) of 0.4 was also noted as a sign of ventriculomegaly in a series of 151 patients by (Marmarou, Young, Aygok et al. 2005). No study in the literature has shown evidence of a positive association with any of the imaging criteria with clinical improvement except a recent study by Marmarou, Young, Aygok et al. 2005. FHI in patients whose condition had improved after drainage and shunt placement, and who had follow-up CT studies from within 6 months to 1 year of surgery showed a reduction in ventricular size and was statistically significant ($p<0.001$). The number of patients who did not improve after External Lumbar Drain (ELD) and shunt placement together with a follow up was small. Some of the findings have been suggested to relate to NPH pathophysiology by comparison made in the pre-shunting CT, e.g. focal sulcal dilation, which has been "misinterpreted" as cortical atrophy in the previous times and therefore even been used as a criterion to exclude patients from undergoing a shunting procedure (Holodny, George, de Leon et al. 1998). Takeuchi et al studied patients with severe cerebral atrophy and found good improvement in 48% following shunting, providing evidence that cortical atrophy does not correlate with outcome. In a study of five cases of patients who presented with focal dilation of cortical fissures and sulci, in three of the cases, there was a paradoxical decrease in the size of the dilated fissures and sulci that paralleled the decrease in the size of the lateral ventricles following successful shunting. The authors concluded that focal fissural and sulcal dilation may represent "atypical" reservoirs of cerebrospinal fluid analogous to the ventricular system (Holodny, George, de Leon et al, 1998). Hydrostatic valves (Dual-Switch-Valves) were implanted in 80 patients with NPH and one year postoperatively Evans-Index was measured. 80% of the patients who showed no postoperative change in ventricular volume had 59% good to excellent clinical improvements, 17% satisfactory clinical improvement, and 24% no improvement. Of the 14% of those who showed moderate reduction in ventricular size 36%

experienced a good to excellent clinical improvement, 28% a satisfactory improvement, and 36% unsatisfactory improvement. A marked reduction in ventricular size was observed in 6% of the patients, of whom, 60% demonstrated good to excellent outcomes, whereas 40% had unsatisfactory outcomes. Favourable outcomes following the implantation of a shunt in patients with NPH did not correlate with decreased ventricular volume 1 year after surgery. In fact, better clinical outcomes were observed in patients with little or no alteration in ventricular size, compared with those in patients with marked decrease in ventricular size (Meier and Mutze, 2004). The same authors reported a similar conclusion in 2003 (Meier, Paris, Grawe, et al. 2003). Most crucial, however, is the accurate selection of those patients, which may benefit from shunting based on both the clinical and imaging findings.

1.4.3. Magnetic resonance techniques (M.R.I)

Multimodal Magnetic Resonance protocols are ideal for investigating the vascular contribution to human brain disease because of the uniquely high resolution, the safety profile and the ability to study subjects longitudinally. Furthermore the ability to co-register high resolution anatomical data with physiological (haemodynamic) and biochemical (lactate and high energy phosphate metabolites) data in the same study provides an unparalleled tool to relate vascular compromise with the metabolic consequences of ischaemia in specific areas of brain.

Current clinical imaging detects areas of ischemic damage both acutely and in the chronic period. T2 weighted changes have been reported as soon as 2 hours after infarction (Mintorovitch, Moseley, Chileuitt, et al. 1991) and are visible years after the infarct has matured. Diffusion weighted imaging has found a use in the early detection of ischemic tissue

which is clearly delineated from unaffected tissue, in the face of unchanged conventional imaging.

1.5. Diagnostic dilemmas

The differential diagnosis of iNPH includes a large number that are relatively commonplace in the elderly (Pickard, 1984). Table 1.1 (page 40) outlines the differential diagnosis for NPH classified by their symptoms. Gait being the commonest and earliest symptom can be put down by most patients as a slowing down process of aging. If they have associated neck and back pain they could have been investigated for spondylotic changes. Only in the later stages when they start developing cognitive impairment with or without urinary symptoms does it raise a suspicion of NPH. As well as gait disturbances, Fisher CM, in 1982 noted that hand tremor; writing disturbances and fine motor activity can also be affected in NPH. These symptoms of tremor could make it difficult to distinguish from Parkinson's disease (PD). Parkinson's disease, even without the tremor and other disorders such as chronic alcoholism and progressive supranuclear palsy (Vanneste, 2000) may display symptoms of NPH, with gait disturbance, urinary incontinence and subcortical mental deterioration. The number of disorders which have similar symptoms to NPH highlights the fact the appropriate clinical evaluation is required to make a diagnosis and also that the classical triad is not unique to NPH.

Deficits associated with NPH tend to be mild to moderate subcortical dementia which are best differentiated from cortical dementia by the absence of aphasia (disturbance in the comprehension or production of speech) apraxia (inability to perform voluntary actions) and agnosia (inability to recognize the form and/or function of objects & people) (Boon, Tans, Delwel et al, 1997). The dementia may also be caused or exacerbated by a number of factors, including ischaemia, frank infarction and relative CSF stasis with decreased clearance of various

macromolecules (Klinge, Samii, Muhlendyck et al, 2003. Silverberg, Mayo, Saul et al, 2003. Tullberg, Hultin, Ekholm et al, 2002.) There have been a number of studies, which have attempted to differentiate the dementia of NPH and Alzheimer's. The dementia in AD is cortical and characterised by impairment in language executive functions, constructional and visuospatial abilities. Impairment of memory, especially for recent events, is the most prominent feature of Alzheimer's. As can be seen these features of Alzheimer's are very similar to those found in NPH. As has previously been reported, evidence of aphasia, is a poor prognostic factor for surgical success and subsequent improvement of the symptoms of NPH (Graff-Radford, 1999). It could therefore be surmised that evidence of aphasia is indicative of AD rather than NPH. To enable clinicians to distinguish NPH from other dementias a number of studies have aimed to assess the nature of the cognitive decline in NPH. Batteries of tests have been used to differentiate the types of dementia as shown in Table 3.4, in section 3.4.1. These tests are designed to assess for dementia, which is subcortical. The prevalence of AD in patients with normal pressure hydrocephalus was found to be related to the severity of dementia. Golomb, Wisoff, Miller et al in 2000 found that those who scored lower on neuropsychological tests and had increased gait disturbance and urinary incontinence; were more likely to have Alzheimer's concomitant with NPH. Following shunt surgery there were no significant differences found in the extent of improvement between those with NPH who had concomitant Alzheimer's and those with NPH only. Both groups were found to significantly improve with regard to gait and incontinence. In accordance with previous findings cognitive impairment was not found to have improved significantly following shunt surgery. This study suggests that improvements in the physical symptoms of NPH can be improved even when the patient also has AD. Several researchers have suggested that those with Alzheimer's should not be selected for surgery.

However, if the shunt alleviates these physical problems caused by NPH, this might reduce the pressure on the families of the patient, even if the dementia were still present. Some authors suggest that AD is quite prevalent in NPH, more so than they conservatively estimated and propose that a dual diagnosis such as this should not prevent the patient from receiving a shunt. Silverberg, Mayo, Saul et al, 2003 postulate a new entity of CSF circulatory failure, with features of AD and NPH. NPH–AD syndrome may cover an important subset of patients who carry the diagnosis of either AD or NPH.

Table 1.1: Differential Diagnosis for Normal Pressure Hydrocephalus classified by their symptoms.

Cognitive and behavioural manifestations
Neurodegenerative disorders:
Alzheimer's disease
Parkinson's disease
Lewy body disease
Huntingtons disease
Frontotemporal dementia
Amyotrophic lateral sclerosis
Spongiform encephalopathy
HIV and Syphilis
Vascular dementia:
Cerebrovascular disease
Stroke
Multi infarct dementia
Binswanger's disease
Vertebro-basilar insufficiency
Cerebral autosomal dominant arteriopathy
Gait and balance disturbances
Structural lesion of brain or spine:
Tumours
Stroke
Vascular malformations
Spinal stenosis
Rheumatoid arthritis
Craniocervical abnormalities
Neurodegenerative disorders:
Idiopathic Parkinson's disease
Amyotrophic lateral sclerosis
Others
Peripheral neuropathy
Urinary disorders
Urinary tract infection
Bladder and prostate enlargement
Benign prostatic enlargement

Other hydrocephalus disorders:
Aqueductal stenosis
Arrested hydrocephalus
Long standing overt ventriculomegaly syndrome
Non-communicating hydrocephalus.
Miscellaneous:
Collagen vascular disease
Epilepsy
Depression
Traumatic brain injury
Chiari malformation
Wernicke's encephalopathy
B12 deficiency
Carcinomatous meningitis

The main differences between NPH, Alzheimer's and Parkinson's are that the postural instability starts early in Parkinson's where as it can be a late presentation in NPH. Patients with Parkinson's have rigidity, tremors and bradykinesia which can also be present in NPH but not as a prominent early feature and rarely seen in AD. Most patients with AD have early onset of memory symptoms, difficulty performing familiar tasks and behavioural changes, whereas these present late or partly in NPH and PD.

1.6. Summary

Historically there has been considerable variation of the results in pathophysiological studies of NPH and in the results of studies attempting to determine the utility of tools to predict outcome from surgery in this condition. This is likely to be related to the range of aetiological factors operative in NPH and therefore heterogeneous patient selection. In addition, partly because NPH is rare, most of the studies in the literature are small and it is difficult to justify the application of the results from small studies into clinical practice. At the same time technological advances mean that different methods have been used to assess the same parameter. This makes comparison between studies more difficult. Additionally, studies that diagnose NPH on the basis of recovery from shunting will inevitably exclude patients with advanced or irreversible disease and may unnecessarily restrict selection of patients to those earlier in the disease course. These studies also ignore the fact that technical factors in shunting contribute greatly to outcome. There is therefore a potential for excluding data from patients who have NPH but who were not adequately treated. If investigators used widely accepted standards in methodology and patient selection, results could be more easily interpreted. Not withstanding these problems, there is evidence that NPH is the consequence of multifactorial processes and there are arterial, venous and CSF hydrodynamic contributions to the disease process. The aetiology of NPH remains

uncertain but the clinical deterioration is probably the result of a combination of both cerebrovascular and pressure effects on the periventricular white matter and deep grey matter structures.

In order to limit the heterogeneity of potential aetiologies biasing results and because the NPH group represents the largest single group of patients with CCH patients with NPH were chosen as a group to study. We have included both iNPH and sNPH in our study.

Chapter 2: Pathophysiological hypotheses

2.1. Histopathology of normal pressure hydrocephalus

There have been very few human studies looking at the periventricular tissues in NPH (Del Bigio, 1993). An early study of two patients with clinical and radiologic criteria for NPH who came to autopsy demonstrated extensive hypertensive cerebrovascular disease in the deep white matter (Earnest, Fahn, Karp, 1974). The meninges and the arachnoid villi were normal in these cases. Another shunt responsive case that came to autopsy was characterized by severe hypertensive vasculopathy with multiple infarcts, which were distributed mainly throughout the periventricular white matter and the basal ganglia (Koto, Rosenberg, Zingesser et al, 1977).

A mixed study of 7 patients with the clinical features of both idiopathic (2 cases) and secondary (5 cases) NPH, demonstrated marked microvascular involvement of the periventricular tissues (Akai, Uchigasaki, Tanaka et al, 1987). There was moderate to severe arteriosclerosis in both periventricular and deep white matter tissues. Demyelination, similar to the ischaemic demyelination of SAE (Binswanger's disease) was present in all cases and microinfarction of the periventricular tissues was commonly found. In addition, there was focal leptomeningeal fibrosis and a reduction in the arachnoid granulations, the structures responsible for re-absorption of CSF into the venous system. One of these cases designated "idiopathic", was young, had a significant history of alcohol abuse and psychiatric disease and may have been more appropriately considered chronic alcoholic encephalopathy. There wasn't enough clinical data given to explore this. He had a poor response to shunting and had the mildest white matter demyelination of the group.

Interestingly, the subependymal tissue in all of these cases was associated with oedema and spongiosis. The ependymal layer was thinned and focal disruption was evident. There was

widespread demyelination within the periventricular white matter with sparing of the arcuate fibres. Focal ballooning of myelin sheaths was seen and axonal loss was observed which was less marked than the demyelination. Despite widespread demyelination there were few macrophages containing fat and myelin debris and astrocytic proliferation was limited. This suggests that the demyelination is not primarily inflammatory in nature. There was variable gliosis and in all but the 16-year-old case, the arteries and arterioles demonstrated marked intimal fibrosis and marked hyalinization of the media. The veins also demonstrated marked fibrosis of the wall and perivascular spaces suggesting that vascular disease in this condition may be a combination of arterial and venous origin.

2.2. Pathophysiological hypotheses

The current understanding of mechanisms responsible for the symptoms in NPH is reviewed below. Although the pathological mechanisms underlying NPH are not fully understood, changes in the perfusion of the periventricular white matter resulting from abnormal CSF hydrodynamics are thought to be important in the genesis of symptoms. Indeed, one view is that a reversible form of ischaemia is the underlying haemodynamic contribution to the disease process (Bateman, 2000). Invasive lumbar infusion studies have demonstrated abnormal CSF hydrodynamic properties in these patients (Vanneste, 2000). In addition, whilst the ICP is normal during the day and hence at LP, invasive monitoring has shown those NPH patients have characteristic repeated, short-lived, nocturnal elevations of pressure, B-waves (Symon, Dorsch and Stephens, 1972. Crockard, Hanlon, Duda et al, 1977. Pickard, Teasdale, Matheson et al, 1980). A further view is that the periventricular tissues are subject to toxic substances in the CSF which is forced into the white matter in the form of transependymal flow (Silverberg, 2004). These putative mechanisms are reviewed below.

2.2.1 CSF hydrodynamic factors and mechanical factors

Hakim and Adams (1973) in their original description of NPH hypothesised that previous pathology was essential in causing an increase in ventricular pressure which in turn leads to ventricular dilatation. This theory states that ventricular pressure and dilatation eventually equilibrate to leave the chronic syndrome we know as secondary NPH. This does not however explain the mechanism in idiopathic NPH. Neither does this theory account for the continuing ventricular dilatation of untreated patients with clinical diagnoses of NPH. The authors also invoked Pascal's Law in explaining the pathophysiology of their newly described condition. This law states "the pressure applied to an enclosed fluid is transmitted undiminished to every portion of the fluid and to the walls of the containing vessel" (Hakim and Adams, 1965).

Mathematically this is expressed as:

Force = pressure x area.

More explicitly, the force applied to the ventricular wall varies with ventricular area, so that patients with normal ventricular area and a normal range opening pressure of 18 cm of water will have a given force acting at their ventricular walls. If the area is doubled the force required to keep CSF pressure at 18 cm of water will also have to double. In other words, the pressure is not a good indicator of force actively compressing the periventricular tissues unless the area of the ventricle is known and the larger the ventricles the larger the forces active at any given opening pressure. Fig 2.1 shows the normal intracranial CSF pathways.

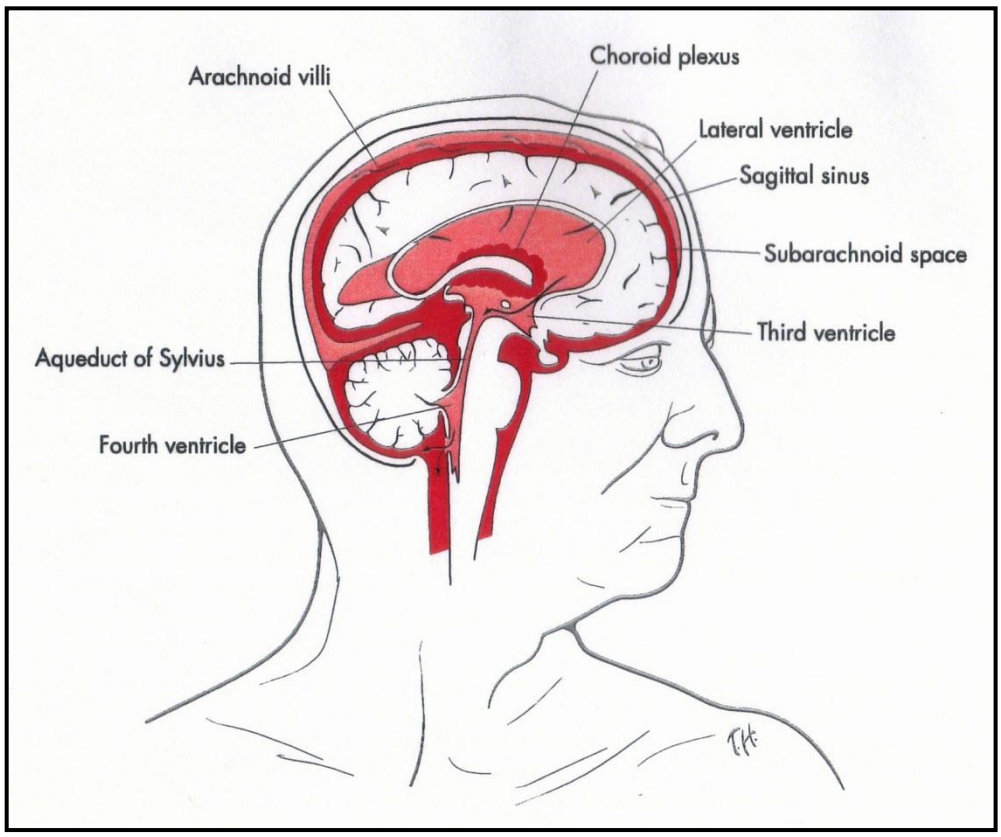


Fig: 2.1 Normal intracranial CSF pathways. (www.lifenph.com/about.asp. Webpage accessed on 20.10.2007)

An analysis of this "total force" hypothesis, however, shows that it does not take into consideration the tensile properties of the wall of the container (Geschwind, 1968). This "container," the brain (and its coverings), is complex and consists of vascular structures and other tissues and the tensile properties of the ventricular wall determine its behaviour in the face of changes in pressure. Any theory regarding the pressure and differential volume changes in the ventricles needs to take into consideration the properties of the ventricular walls (Geschwind, 1968).

Other authors have proposed that the primary pathology in the CSF circulatory system is coeternal (Lying-Tunell, 1977) or supra-Sylvian (Kitagaki, Mori, Ishii et al, 1998) block to the outflow of CSF leading to a pressure gradient between the ventricle and the convexity or a

transmantle gradient (Conner, Foley, Black et al 1984). Supra- Sylvian block was inferred from Magnetic Resonance Imaging (MRI) analysis of the pattern of focal dilatations of sulci in 11 patients with iNPH compared to 11 patients with AD. No pressure measurements, however, were taken (Kitagaki, Mori, Ishii et al, 1998). The transmantle gradient has only been demonstrated in 7 cats with kaolin induced hydrocephalus (Conner, Foley, Black et al 1984) and has not been replicated in humans.

According to this line of thought the gradient between ventricle and convexity may be constant, with pressures within normal ranges, or intermittent (Geschwind, 1968) and leads to dilatation of the ventricles. This then in turn causes stretching of neural or vascular structures and therefore symptoms. Neural structures suggested include primary motor, supplementary motor, sensorimotor integration loops, ascending and descending pathways, extra pyramidal centres or autonomic centres. The postulated effect may either be diffuse, affecting sensorimotor integration or via specific pathways such as the medial fibres of the corona radiata (Fisher, 1982. Hennerici, Oster, Cohen et al, 1994) which when damaged lead to the "magnetic gait" disturbance seen in this and other conditions. Impaired input from sensorimotor, anterior cingulate and superior frontal cortex to the brainstem reticular formation may contribute to the impaired initiation and maintenance of gait and the stance disorder (Nutt, Marsden and Thompson. 1993), which characterises the gait in NPH. Pressure on the deep grey matter structures, and the interconnections between the basal ganglia and the motor and supplementary motor areas have also been thought to result in the Parkinsonian features sometimes seen in this condition (Thompson and Marsden. 1987) Psychomotor retardation may be the result of pressure effects on the fibres of the frontal corona radiata; specifically, the longitudinal fibres of the superior frontal gyrus (Fisher, 1982)

Impaired ability to absorb CSF or increased resistance to CSF outflow (Rout) is likely to contribute to the pathophysiology of NPH. In a study of 15 patients with NPH, 8 of who were considered idiopathic the Rout was measured using a constant flow and pressure lumbo-ventricular study (Borgesen, Gjerris and Srensen, 1978). Interestingly, the patients with an identifiable cause for their NPH tended to have higher resistance to outflow than the apparently idiopathic group. This suggests that patients with secondary NPH are likely to have a primary difficulty with CSF re-absorption as a consequence of their original illness.

An inability to clear potentially toxic metabolic products, such as amyloid ß-peptides tau protein, could lead to an increase in their concentration in brain interstitial fluid, creating a potentially decrease neuronal function and survival. In NPH and in normal ageing, there is evidence for both a decrease in CSF production and an increase in the resistance to CSF absorption (Czosnyka, Whitehouse, Smielewski et al., 1996, Silverberg, Huhn, Jaffe et al, 2002). Both events lead to a decrease in CSF turnover and, in turn, a decreased clearance of amyloid ß-peptides tau proteins is suggested by the higher than expected coincidence of Alzheimer's disease pathology in cortical biopsies taken from NPH patients at the time of shunt implantation. From 30 to 50% of NPH patients will exhibit plaques and tangles consistent with Alzheimer's disease, and, in the severely demented NPH patients, 75% will show Alzheimer's disease (Silverberg, May, Saul et al, 2003). In the Dutch NPH study, increased Rout correlated with a good outcome from shunting with a positive predictive value of 92% for patients with an Rout of greater than 18 mmHg/ml/minute (Boon, Tans, Delwel et al, 1997)

The CSF circulatory system is subject to senescence (Rubenstein, 1998) and Rout is known to increase with age (Albeck, Skak, Nielsen et al 1998). How Rout is related to ventricular dilatation and the genesis of symptoms in NPH is still not clear. It is likely that these

senescent changes may be exaggerated in some patients with iNPH and contributes to both the increased Rout and to intermittently raised ICP. Intermittent peaks of ICP commonly in the form of nocturnal B waves have been demonstrated in NPH (Symon, Dorsch, Stephens, 1972), but are also seen in normal physiology (Martin, 1978). B-waves occur at 0.5 to 2 per minute and are of variable height from just discernible to 50 mmHg (Martin, 1978). Frequent B waves predict a good outcome from shunting (Crockard, Hanlon, Duda et al, 1977. Pickard, Teasdale, Matheson et al, 1980. Symon, Dorsch, 1975). In one study 8 patients with NPH exhibited resting ICP of 11.7+/-6.7 mmHg with ICP waves of 17.1+/-8.9mmHg 41.5% of the time studied (Crockard, Hanlon, Duda et al, 1977). In another study of 26 patients with NPH, 8 of whom where idiopathic, the mean ICP in shunt responders was 12.5+/- 6mmHg and 7.5+/- 2mmHg in non-responders (Pickard, Teasdale, Matheson, et al. 1980). Other workers have found that good outcome was associated with other measurable changes in B-waves such as higher amplitude B waves. This was demonstrated in a study of 23 shunted patients with iNPH in which the amplitude was greater than 9 mmHg (Raftopoulos, Deleval, Chaskis, 1994)

Intermittent peaks of ICP may have a pathological effect by other means than dilatation. Pathological activity may also be mediated through pulse waves or the water-hammer effects (Bering, 1955. Bering, 1962). This was first identified as a possible mechanism by Bering who noted asymmetric ventricular dilatation following unilateral choroid plexotomy in an experimental model (Bering, 1955). The contralateral lateral ventricle dilated to a larger extent than the ipsilateral lateral ventricle when hydrocephalus was induced by kaolin injection. In addition, the systolic wave of ICP, which is a consequence of the systolic wave of blood entering the brain, may be responsible for ventricular dilatation by producing endoventricular pressure pulses (Di Rocco, 1984). In a series of experiments on lambs, Di Rocco demonstrated the effect

of endoventricular CSF pressure pulses on ventricular dilatation. One group of animals were subject to intermittent peaks of CSF pressure mediated by a unilateral intraventricular balloon in one of the lateral ventricles. The peaks were timed with the systolic pulse and 2-hour periods of this intervention on alternate days up to a maximum of 26 hours were delivered. Ventricular dilatation occurred rapidly and the histological changes of the ependyma and periventricular tissues included denuding of the ependymal layer with pallor of the periventricular tissues associated with demyelination (Di Rocco, 1984). These findings are similar to those found in patients with NPH. It remains unclear, however, which feature of ICP is the crucial pathological factor and ICP monitoring is invasive and requires expertise. These problems of interpretation and data ascertainment unfortunately confine this technique to being a research tool for the time being.

Hakim and Adams (1973) described this syndrome after observing a clinical improvement after removal of CSF. A positive "tap test" is where 20 to 30 mls of CSF removed at lumbar puncture is associated with a rapid improvement of gait and or mentation within minutes to hours. A positive tap test suggests that recovery occurs due to mechanical release from pathology such as a release of hydrostatic pressure on stretched axons post procedure and therefore supports a stretching hypothesis associated with ballooning of the ventricles. It is not clear, however, how pressure effects or stretching of neural pathways causes dysfunction of neural transmission which is as rapidly reversible as is suggested by the marked improvement in function patients can get with the tap test. If stretching or pressure on neural pathways was the operative mechanism in NPH a correlation between ventricular size and disability would be expected and recovery post shunting would correlate with reduction in ventricular volume. In fact neither the first nor the second condition is consistently observed. If stretching is an

important mechanism how can the striking phenomenon of asymptomatic ventriculomegaly be explained? In a study of 45 patients with iNPH ventricular size did not correlate with response (Petersen, Mokri, Laws, et al, 1985).

Intriguingly, the tap test procedure is associated with a high false negative rate (Vanneste, 1994) and a different mechanism must account for symptoms in patients with negative tap tests that respond to shunting, such as remyelination. An alternative explanation of the positive tap test is that ventricular dilatation may have an impact on the periventricular microcirculation. If it is assumed that disruption of association pathways in the periventricular tissues is at the core of the pathology in NPH, it is probably not a co-incidence that white matter autoregulation of blood flow is significantly less efficient than that in grey matter (Symon, Pasztor, Dorsch et al, 1973) and that the anterior and posterior periventricular tissues occupy an arterial watershed area (De Reuck, 1971. Howard, Trend, Russell et al, 1987. Bladin and Chambers, 1993), a venous watershed (Andeweg, 1996) and an area of increased biomechanical stress in an expanding ventricle (Pena, Bolton, Whitehouse et al, 1999).

2.2.2 Cerebrovascular factors

2.2.2.1 Arterial considerations

Cerebrovascular effects are thought to contribute to the clinical picture in iNPH. Proposed mechanisms include reversible ischaemia due to stretching of the anterior and or middle cerebral arteries, compression of vascular beds and to reduced cerebral blood flow and volumes (Greitz , Grepe , Kalmer et al, 1969. Mathew, Meyer, Hartmann et al, 1975. Ingvar, Risberg, Schwartz et al, 1975) and impaired autoregulation. Patients with NPH have been shown to have more cardiovascular risk factors than age matched controls (Graff-Radford and

Godersky, 1987. Casmiro, D'Alessandro, Cacciatore et al, 1989. Krauss, Rege, Vach et al 1996). In one-study 14/19 (74%) patients with iNPH had systemic hypertension while 10 of the 14 shunt responders had systemic hypertension (Graff-Radford and Godersky, 1987). The best estimate of prevalence of hypertension, both treated and untreated for this age group in the USA was quoted at 35% for men and 34% for women aged 60 to 69 (Graff-Radford and Godersky, 1987). In another study 17 patients with iNPH were compared with age and sex matched controls (Casmiro, D'Alessandro, Cacciatore et al, 1989). In this study an odds ratio of 3.14 was calculated for hypertension in this condition and 4.2, and 6.0 for ischaemic heart disease and diabetes respectively. In another study of 65 patients with iNPH a highly significant association with arterial hypertension was demonstrated with 83% of patients with iNPH suffering hypertension compared to 36% of controls (Krauss, Regel, Vach, et al 1996). Diabetes was also significantly associated with iNPH and was present in 49% of patients and 29% of controls.

Evidence of reduced blood flow in different regions of the brain in patients with NPH has been demonstrated using single photon emission computed tomography (SPECT) (Mathew NT, Meyer JS, Hartmann, et al, 1975. Graff-Radford, Rezai, Godersky, et al 1987. Vorstrup, Christensen, Gjerris, et al 1987. Kimura, Tanaka, Yoshinaga et al, 1992. Waldemar, Schmidt, Delecluse, et al 1993. Larsson, Bergh, Bilting, et al, 1994. Kristensen, Malmo, Fagerland, et al, 1996. Tanaka, Kimura, Nakayama et al, 1997). Fifteen patients with idiopathic (Vanneste, Augustijin, Dirven, et al 1992) and secondary (Gustafson and Hagberg. 1978) NPH had regional cerebral blood flow and regional cerebral blood volume measurements performed before and after CSF pressure was lowered at lumbar puncture (Mathew, Meyer, Hartmann et al, 1975). Maximal reductions in these haemodynamic variables was in the territory of the anterior cerebral

artery and CSF pressure reduction at lumbar puncture lead to a significant rise in these variables in contrast to a non hydrocephalic demented control group.

Using a tomographic technique regional cerebral blood flow (rCBF) was measured in 22 patients with NPH (Graff-Radford, Rezai, Godersky, et al 1987). Pre-operative reductions in rCBF were most prominent in anterior regions and improved at 2 months post operatively. It was not clear from this study how many patients were idiopathic and how many secondary. An anterior to posterior ratio of blood flow (1.05) was used to correctly distinguish between good and poor outcome groups with the good outcome ratio being less than 1.05. Interestingly the improvement in rCBF was not sustained at 6 months.

In a further study of rCBF in a mixed group of 17 patients with NPH (14 idiopathic) a central low flow area was described which significantly reduced on shunting in 6 patients (Vorstrup, Christensen, Gjerris, et al 1987). All six of these patients improved clinically. A quantitative three-dimensional technique using xenon-enhanced computed tomography was applied to seven patients with NPH secondary to subarachnoid haemorrhage (Kimura, Tanaka, Yoshinaga, 1992). Thalamic and frontal subcortex regions demonstrated the greatest reduction in rCBF (47.3% and 39.1% vs control) pre-operatively and shunting lead to recovery of rCBF most impressively in the frontal subcortex (95.7% of control values). The improvement in rCBF correlated with reduction in ventricular size, resolution of periventricular lucency and clinical improvement.

Subsequent studies using different techniques confirmed a sub-cortical low flow region (Waldemar, Schmidt, Delecluse, et al. 1993) or reduced frontal white matter rCBF (Larsson, Bergh, Bilting et al, 1994) pre-operatively which recovered after shunting. In another study of

31 individuals with iNPH a significant reduction in subcortical white matter rCBF was demonstrated with SPECT (Kristensen, Malm, Fagerland et al, 1996), similar to that demonstrated by the Cambridge group in 2004. They showed maximal decrease in the ventricular wall, with an increase in cerebral blood flow (CBF) as one moves laterally. Among subjects with NPH, a more profound decrease in CBF followed the induction of increased CSF pressure, in a U-shaped distribution, with the CBF shifting laterally from the ventricle by approximately 9 mm and normalizes as it moves toward the cortex. Cerebral vascular autoregulation was also impaired among these subjects, suggesting less capacity to compensate for increases in CSF pressure (Momjian, Owler, Czosnyka et al, 2004). If reduced cerebral blood flow was the only determinant in the disease process a correlation between severity of flow deficit and symptoms would be expected. No such correlation has been demonstrated to date and attempts to use these techniques to predict outcome from surgery, have met with mixed success (Owler, Pickard, 2001). This is probably because, although subcortical low flow regions are common in NPH and potentially important in the disease process, there is no straightforward link between low blood flow and clinical deterioration (Mamo, Meric, Ponsin et al, 1987). An additional consideration is that low CBF may be secondary to a primary metabolic impairment as has been the interpretation of results in positron emission tomography (PET) studies in Alzheimer's disease. SPECT techniques have demonstrated focal reductions in rCBF in the posterior parietal and contiguous temporal and occipital regions in patients with Alzheimer's disease (Talbot, Lloyd, Snowden et al, 1998).

PET studies investigating the rCBF in patients with NPH (Brooks, Beaney, Powell et al, 1986. Klinge, Berding, Brinker et al, 1999) have demonstrated global white matter oligaemia pre-operatively. One PET study found appropriate levels of oxygen extraction for the reduced

cortical blood flow in chronic hydrocephalus (Brooks, Beaney, Powell et al, 1986). This contrasted with the acute hydrocephalus group in which the reduced blood flow was accompanied by an elevated oxygen extraction value. This suggested that the acute hydrocephalus group was compensating for the oligaemia whilst the chronic group was not able or did not need to compensate for oligaemia by increasing oxygen extraction. Another study demonstrated a marked reduction in the white matter rCBF (40 ml/100ml/minute) in a group of 10 patients with chronic hydrocephalus compared to 10 controls (61 ml/100ml/minute) (Klinge, Berding, Brinker et al, 1999). The control group, however, in this study was much younger than the patient group (25 vs 67 yrs respectively).

If low rCBF is not solely responsible for the clinical deterioration then reduced autoregulation may be partly responsible for the symptoms. Autoregulation is the maintenance of rCBF despite variation in systemic arterial blood pressure between 50 and 150 mmHg provided the carbon dioxide ($CO_{2)}$ tension is normal (Strandgaard, Olesen, Skinhoj et al, 1973). Evidence for impaired autoregulation is provided by a number of studies which measured rCBF pre- and post- tap test (TT) (Mathew, Meyer, Hartmann et al, 1975. Mamo, Meric, Ponsin et al, 1987. Meyer, Tachibana, Hardenberg et al, 1984) or shunting (Graff-Radford, Rezai, Godersky et al, 1987. Vorstrup, Christensen, Gjerris et al, 1987. Kimura, Tanaka, Yoshinaga, 1992. Waldemar, Schmidt, Delecluse, et al. 1993. Larsson, Bergh, Bilting et al, 1994. Tanaka, Kimura, Nakayama et al, 1997) and found an increase in rCBF after CSF diversion. Only two studies failed to show changes in CBF post-TT (Kristensen, Malm, Fagerland et al, 1996. Kushner, Younkin, Weinberger et al, 1984). Both rCBF and rCBV increased after tap testing. Xenon inhalation was then used to demonstrate an increase in blood flow in frontal and temporal grey

matter in 11 patients with NPH following CSF pressure reduction at lumbar puncture (Meyer, Tachibana, Hardenberg, et al. 1984

In a further 25 patients with NPH (18 idiopathic) intravenous Xenon and gamma camera were used to demonstrate an improvement in hemispheric blood flow 3 hours after removal of 20 to 30 mls of CSF at lumbar puncture (Mamo, Meric, Ponsin et al, 1987). This contrasted with findings from a group of "control" patients with senile and "pre-senile" dementia who underwent blood flow measurement before and after CSF removal and in whom the hemispheric blood flow reduced or remained unchanged.

There was a positive correlation between reduction in ventricular size and increase in blood flow in a study but changes in blood flow did not correlate with changes in function (Vorstrup, Christensen, Gjerris et al, 1987).

Klinge, Berding, Brinker, et al. 1999 demonstrated in a PET study of patients pre and post-operatively where the patients who responded to shunting also improved their cerebrovascular reserve to 52% at 7 days. There was no difference in cerebrovascular reserve between good and poor outcome groups prior to surgery and the poor outcome group was characterized by a post-operative reduction in cerebrovascular reserve.

Much of the discrepancy between studies can be accounted for by heterogeneous group selection, differing techniques and poor white matter resolution. The techniques discussed above are biased by, if not wholly dependent on, cortical signal. It is also worth bearing in mind that various essential neuronal functions are tightly coupled to thresholds of cerebral blood flow (Astrup. 1982) and that patients with iNPH may have impaired autoregulation and white matter circulation. This may make patients with iNPH more susceptible to abnormal ICP fluctuations

which may have an exaggerated impact on the already oligaemic white matter microcirculation resulting in intermittent ischaemia. This dual pathology model may provide the extra element required to explain the paradox that the white matter is oligaemic in iNPH but the level of oligaemia is not predictive of outcome from surgery. If there is obligate marginal perfusion in the background of iNPH other active processes may be required to embarrass perfusion to ischaemic levels such as abnormal ICP peaks and/or CSF absorption. These processes could theoretically be independently or collectively active in each case of NPH.

2.2.2.2. Venous hypotheses

The periventricular tissues are supplied by long medullary arteries and drained exclusively by the deep venous systems, which terminate in the straight sinus. The centrum semiovale occupies an area within the venous watershed, which has been demonstrated between the territories of the deep and the superficial venous systems (Andeweg, 1999). The importance of this venous watershed is that there are no anastamoses between deep and superficial systems and that differential involvement of each system may play a part in the pathophysiology of different conditions ranging from NPH and Alzheimer's disease to benign intracranial hypertension (Bateman, 2003). It has been argued that as a consequence of the watershed area differential effects on the compliance of each system can result in intraparenchymal pressure gradients leading to ventricular enlargement in NPH and ventricular compression in benign intracranial pressure (Bateman, 2003). A reduction in vascular compliance in the superficial venous system in 10 patients with NPH (Bateman, 2000) has been demonstrated using magnetic resonance flow quantification of the cerebral vessels. This impaired superficial compliance, a consequence of CSF pulsation on subarachnoid veins, leads to increased resistance to venous flow and therefore pressure in these vessels. This in turn would lead to increased capillary

pressures and therefore production of interstitial fluid which would communicate with the CSF via the perivascular spaces. Bulk flow would transport CSF and therefore isotope in scintigraphy studies from the vertex to the ventricles where the compliance of the deep system remained normal. Because there is little interaction between CSF and venous outflow at the vein of Galen the pressure in the deep system is invariably lower than CSF pressure. This leads to a transependymal pressure gradient and ventricular enlargement. This neatly explains the commonly observed discrepancy between cortical and ventricular dilatation in NPH.

2.2.3. Metabolic dysfunction in hydrocephalus

Haemodynamic compromise may be expected to result in metabolic disruption. Ischaemia results in mitochondrial dysfunction and cellular damage and repair may result in lasting metabolic changes. This area has not been studied in patients with iNPH to any great extent. Most of the work that has been done on hydrocephalus has been done in acute hydrocephalus, in children, and animal models of acute hydrocephalus. This is now reviewed.

The main issues studied in animal models of acute hydrocephalus with magnetic resonance spectroscopy techniques concern changes in metabolite levels as a consequence of ischaemic processes or osmolyte compensatory change. A comprehensive biochemical and physiological study used cats, rabbits and rats rendered hydrocephalic using kaolin injections (Higashi, Asahisa, Ueda et al, 1986). In the acute and chronic (6-8 weeks) stages rCBF was globally reduced whilst CO_2 reactivity of CBF was reduced only in the acute stages. Water content of the periventricular tissues increased in the acute phase only and lactate was temporarily detected in the frontal tissues during the acute phase of the experiment. Adenosine triphosphate (ATP) was reduced in all tissues in the acute phase. There was recovery to pre-

hydrocephalic levels and then another reduction in ATP levels in the chronic phase. In addition cholesterol levels dipped after the acute phase and remained reduced in animals with the most severe hydrocephalus. Catecholamine and monoamine metabolites were significantly increased in the chronic phase of the experiment in all tissues. This change in neurotransmitter metabolites was attributed to an unexplained effect of hydrocephalus on the function of the major neurotransmitter pathways in this condition.

Anaerobic glycolysis has been demonstrated in deep white matter in an acute model using an autoradiographic method in kittens (Chumas, Drake, Del Bigio et al, 1994). Glucose utilization in the cortical grey matter regions remained unaffected. These findings have been replicated and refined by further studies using magnetic resonance spectroscopy techniques. Phosphorus spectroscopy in a neonatal model of acute hydrocephalus confirmed the importance of acute ischaemic processes by demonstrating a reduced whole brain PCr/Pi and an increased Pi/ATP ratio (de Silva, Drake, Lemaire et al, 1994). These changes in high energy phosphate metabolites are characteristic of acute ischaemia. There were no significant changes in intracellular pH either at one or three weeks post induction of hydrocephalus. This was explained as indicating post-ischaemic metabolic change as opposed to acute ischaemia. The same group used an autoradiographic method to document reduced periventricular rCBF and recovery with shunting using the same model (de Silva, Michowicz, Drake et al. 1995). This confirms the importance of the periventricular tissues as a site of active pathology in hydrocephalic processes. Another study using both proton and phosphorus spectroscopy in a similar model found that lactate accumulated in whole brain and the PCr/Pi ratio was reduced acutely (Braun, Dijkhuizen, de Graaf et al, 1997). Quantitative in-vitro spectroscopy studies using an inherited infantile hydrocephalus model in rats has confirmed and extended the

understanding of the effects of acute hydrocephalus on the developing brain. Both high energy phosphorus and membrane phospholipid metabolites were reduced in acute hydrocephalus. Shunting early led to recovery of the energy metabolites (Harris, Plant, Briggs et al, 1996). Similarly, in vitro proton spectroscopy in the same model demonstrated a marked reduction in creatine (Cr), N-acetyl Aspartate (NAA) and choline (Cho) amongst other compounds consistent with neuronal atrophy rather than acute ischaemia (Harris, Plant, Inglis et al, 1997). Early shunting resulted in maintenance of the concentration of these compounds whereas a delay led to persistent reductions of NAA indicating a loss of neurons.

A role for ischaemia in humans with NPH is further supported by a phosphorus spectroscopy study, which demonstrated metabolic dysfunction resulting in acidic periventricular tissues (Arnold, Shoubridge, and Villemure, 1988). Similar findings were seen in a mixed group of 5 patients with obstructive and communicating hydrocephalus. The acidic tissues reverted to normal after shunting in the two cases (both obstructive cases) studied post–shunting (Brooke, Ouwerkerk, Adams et al, 1992).

A PET study investigated rCBF and oxygen extraction in patients with hydrocephalus (Brooks, Beaney, Powell et al, 1986). A small number of chronic idiopathic hydrocephalic patients were studied and the baseline measurements were not significantly different from the control group and there was no change with surgery. The acute hydrocephalic group, on the other hand, had inappropriately high oxygen extraction values for the reduction in CBF and this improved with shunting. This is consistent with acute ischaemic process being active in the acute rather than chronic hydrocephalus.

CSF metabolites have also been studied in NPH. Glial fibrillary acidic protein (GFAP) a marker of astrogliosis and neurofilament triplet protein (NFL) a marker of axonal damage, were found to be elevated in 65 (1/3 of whom were idiopathic) patients with NPH (Tullberg, Rosengren, Blomsterwall, et al. 1998). There was a correlation between NFL, a structural component of neurons and a biochemical marker of neurodegeneration, and symptom severity. In addition, high CSF NFL concentrations were associated with high levels of gait and psychometric impairment, urinary incontinence and good outcome from surgery. The same group was able to distinguish 43 patients (49% idiopathic) with NPH from 19 patients with subcortical arteriosclerotic encephalopathy (SAE) by using a marker of demyelination glycosphingolipid (sulfatide) (Tullberg, Mansson, Fredman et al, 2000). Sulfatide was found to be 6 times higher than control in patients with SAE and normal range in patients with NPH suggesting that the pathological substrate of SAE is demyelination and axonal degeneration in NPH. In this study, however, the NPH patients were a mixed group with both secondary and idiopathic patients represented and it is not clear whether ischaemic demyelination is more important in either the idiopathic group than the secondary group. The histopathology data, however, suggests that ischaemic demyelination plays a prominent role in the pathological process in iNPH.

A further study of 14 patients (13 idiopathic) with NPH investigated the changes in CSF levels of somatostatin (SOM), neuropeptide Y (NPY), and corticotrophin releasing factor (CRF) after surgery from pre-operative levels (Poca, Mataro, Sahuquillo et al, 2001). SOM is a neuropeptide found in cortical neurons and hypothalamic neurons, which have been shown, the author's state, to be selectively damaged in hydrocephalus and NPY and CRF are also neuropeptides associated with enhanced cognitive performance. All three of these metabolites

were elevated post-operatively in all patients. This was interpreted as restoration of metabolite levels in the CSF to pre-morbid levels as previous studies had demonstrated reduced levels of these metabolites in NPH. There was no change in cognitive function, however, to parallel the restoration of neuropeptide levels. The use of CSF metabolites to unravel the pathophysiology of NPH therefore remains uncertain.

2.2.4 White matter hyperintensities and transependymal flow

White matter hyperintensities (WMH) are areas of high signal change on T2 weighted MRI sequences. They are common in the periventricular regions in NPH, in the normal elderly and in Subcortical Arteriosclerotic Encephalopathy (Bradley, Whittemore, Watanabe et al 1999). Leucoariosis is a term, which describes radiolucent areas of white matter on CT. It is a term used interchangeably with WMH on magnetic resonance scanning. WMHs have been demonstrated in about 25% of subjects over 65 years of age in a sample of 111 subjects from a large population based study (Breteler, van Swieten, Bots et al, 1994). WMHs are a recognised association of hypertension where the cerebral vessels are found to have hyaline changes in their walls (Pantoni and Garcia, 1997). The histopathological correlates of asymptomatic WMH on T2 weighted images are non-specific and include vascular ectasis, arteriosclerosis, dilated perivascular spaces, demyelination, hyalinosis, and small infarctions.

Asymptomatic WMH (asymptomatic leucoariosis) are more common in subjects with cerebrovascular risk factors and abnormal microvascular function is thought to contribute to the genesis of these features on MRI (Meguro, Hatazawa, Yamaguchi et al, 1990).

In iNPH WMH in the periventricular tissues are more common than would be expected for age (Krauss, Regel, Vach et al, 1997). WMH have been credited with a pathogenic role in

this NPH (Bradley, Whittemore, Watanabe et al, 1999). In this study deep white matter hyperintensities were found in 58% of patients with iNPH compared to 24% in the control group. It was proposed that deep WMH result from ischaemic damage, which reduces the tensile strength of the brain parenchyma thereby setting up a hydrodynamic cycle, which results in ventriculomegaly. This contrasts with the negative correlation between ventricular dilatation and severity of WMH demonstrated above (Krauss, Regel, Vach et al, 1997). It has been suggested that WMH at the horns of the ventricles that are commonly seen in patients with NPH may be an indication of ischaemic damage but that the relationship between vascular disease and NPH is non-causal (Krauss, Regel, Vach et al, 1997).

WMH have been associated with a good response to shunting in some studies (Borgesen, Gjerris. 1982. Jack, Mokri, Laws, et al, 1987). In a large early study 80 patients with NPH (40 idiopathic) 16 patients had periventricular lucencies on CT. All of these 16 patients improved post shunting (Borgesen and Gjerris, 1982). In a further study designed to determine MR signs to distinguish between different dementia diagnoses 17 patients with NPH, 8 patients with obstructive hydrocephalus 8 patients with Alzheimer's disease and 21 with non-Alzheimer's dementia were studied (Jack, Jr., Mokri, Laws, et al, 1987). There were no distinguishing features between the categories of dementia. In addition, patients with more marked periventricular hyperintensity and less marked white matter hyperintensities tended to have a good outcome from shunting, confirming the importance of topographical location of WMH.

Another study confirmed that the presence of moderate to severe white matter lucencies on CT was associated with poorer surgical outcome (Boon, Tans, Delwel et al, 1999). A final study used a more sophisticated semi quantitative scale which incorporated size and shape to quantify the extent of WMH in 34 patients with NPH (Tullberg, Jensen, Ekholm et al, 2001), 13

of whom had iNPH. WMH extent did not correlate with outcome, but clinical improvement had a positive correlation with reduction in the periventricular hyperintensities post-operatively. In addition, only the irregular periventricular hyperintensities at the frontal horns of the ventricles reduced post-operatively. In practice, extensive WMH on imaging is associated with worse surgical outcomes but in itself should not be used as an absolute contraindication to surgery (Krauss, Droste, Vach, et al. 1996. Tullberg, Jensen, Ekholm et al, 2001).

An alternative explanation that warrants consideration is that in NPH WMH may represent increased transependymal flow (Weller and Mitchell 1980. Sato, Ohya, Nojiri et al, 1984. Tamaki, Shirakuni, Ehara et al, 1990). This undoubtedly occurs in animal models of acute hydrocephalus but has not been demonstrated to be the main cause in the elderly patients with normal range CSF pressures. If this was the primary mechanism, one might expect there to be a positive correlation with good outcome from shunting and resolution of WMH on shunting. This has not been demonstrated (Tullberg, Jensen, Ekholm et al, 2001). If WMH represented infarcted white matter or irreversible periventricular damage, on the other hand, the outcome would be expected to be less good the more infarcted tissue there was. In keeping with this hypothesis there is, as mentioned above in fact, a negative correlation between severity of WMH and outcome (Krauss, Droste, Vach et al, 1996). Patients with iNPH who had more extensive periventricular WMH had poorer outcomes than those with smaller volumes of WMH, although some patients with significant WMH volumes who were operated on also had good outcomes from surgery (Krauss, Droste, Vach et al, 1996 Tullberg, Jensen, Ekholm et al, 2001).

The histopathological correlates of asymptomatic WMH on T2 weighted images are non-specific and include vascular ectasis, arteriosclerosis, dilated perivascular spaces, demyelination, hyalinosis, and small infarctions. This suggests that T2 weighted WMH in NPH reflect a

spectrum of disease ranging from reversible to irreversible which may therefore result from a spectrum ranging from microvascular disease to frank infraction.

2.3 Summary

The various hypothesis mentioned in this chapter explains the multifactorial complex nature of the disease. Understanding the natural history has helped us to identify factors that are more specific to NPH. Although various pathologies may co-exist identifying those symptoms that are treatable is essential. In the last 4 decades researchers have helped to identify specific tests that may differentiate the various pathologies that may be involved in the disease presentation. These tests are based on differentiating NPH from other conditions that mimic this group of patients. In the following chapter the aims and methods of trying to identify those patients who are more likely to suffer from NPH and may respond to shunt surgery is explained.

Chapter 3: Aims and Methods

3.1. Introduction

Despite the advances and our understanding of NPH identifying those who may respond to a shunt in a clinical setting is challenging because of the nature of presentation. Prognostic value of CT or MRI on their own is limited and other supplemental tests are necessary to increase the prognostic accuracy of identifying those who may respond to a shunt. Improvement in neuropsychological gait and urinary symptoms following drainage of fixed volume "tap test" or continuous volume of CSF "external lumbar drain" (ELD) can be one method of predicting a quick response. The methods used by researchers in differentiating and identifying those who would benefit from surgery can be complex. There is a large battery of tests available in the literature, all used for differentiating NPH from other conditions and also identifying the shunt responders. Some of these methods need specialist expertise and there are large costs involved. In this study a protocol has been derived from the literature that can be used in a clinical setting that is cost effective, simple and reproducible. The aims of this study are outlined in this section followed by an explanation of the methods chosen to investigate. There are several other aspects of NPH, which were also examined.

3.2. Aims of Study

The aims of this study are listed below; each of these aims will be discussed in the relevant sections in the results and discussion chapters.

1. To compare the demographic and clinical characteristics of patients who are selected for shunting with those who are not. This may provide clearer criteria to distinguish patients

suffering from NPH from those who may be suffering from other disorders from their presentation.

2. To evaluate the usefulness of the CT scan in identifying and preventing complications and predicting outcome at 1 year between the shunted and the non-shunted patients.

3. To evaluate the baseline values of the screening, neuropsychological and gait tests at presentation to determine whether there were any significant differences between the shunted and the non-shunted patients.

4. To evaluate the usefulness of Rcsf value as a criteria for shunting and analyse the outcome of the shunted patients.

5. To determine whether the effects of external lumbar drain (ELD) on supplemental neuropsychological and gait tests in addition to urinary symptoms would identify those patients who would benefit from a shunt, and to determine if there was any correlation between the tests used to select patients for shunting at 1 year.

6. To examine the effects of shunting to determine whether the symptoms of NPH improve following surgery. Where possible, a control group (those not receiving a shunt) were reassessed after the same time period to determine which factors alter over time.

7. To compare the selection criteria including ELD, Rcsf values and outcome of the shunted patients who have responded well to surgery, with those who show little or no improvement. Within group analysis may assist in developing criteria, in the future, to select patients who are most likely to benefit from surgery.

8. To investigate if the neuropsychological and gait tests are able to predict surgical success or failure.

9. To identify the complications occurring from external lumbar drain, shunt and use of anticoagulants.

10. To identify the value of using the programmable shunts.

3.3. Protocol

In this section a review of the inclusion and exclusion criteria for those patients referred with a clinical and radiological suspicion of NPH is discussed. The management protocol used to investigate those who may benefit from a shunt operation is discussed.

3.3.1. Eligibility criteria

3.3.1.1. Inclusion criteria

1. Clinical symptoms of Normal Pressure Hydrocephalus – Dementia, incontinence, gait and other disturbance.
2. Radiological evidence of communicating hydrocephalus (CT or MRI).
3. Both iNPH and sNPH patients were included.

Patients with suspected NPH were admitted to the ward for evaluation accompanied by a family member or carer. They were sent an information leaflet (Appendix 1) giving an overview of what to expect during their stay in hospital. A covering letter was sent emphasising the presence of a family member where possible to provide a detailed history of the patient's symptoms. Patients and their relatives were involved in all decision making. Detailed discussion regarding the nature of their condition, difficulty with diagnosis, investigations, risks and benefits of shunt insertion were discussed. After obtaining a detailed history and completing a

physical examination, CT or MR imaging was reviewed with a radiologist. When there was a suspicion of a co-existing diagnosis the patient was referred to a specialist for an opinion or for further investigation. Those patients who were excluded from the study were further investigated as appropriate or referred to other specialists before reconsidering them. At this point some of the patients were excluded from the study.

3.3.1.2. Exclusion criteria

1. Severe co-morbid factors or contra indications for shunt surgery.
2. Refusal to undergo investigation or surgery for any reason at the first consultation.
3. Reduced life expectancy (malignancy or debilitating disease).
4. Another identifiable cause, other than NPH for their symptoms.

3.3.2. Study design

Following a detail history of the patient's complaints and presentation they underwent a battery of neuropsychological and gait tests as listed in Table 3.1.

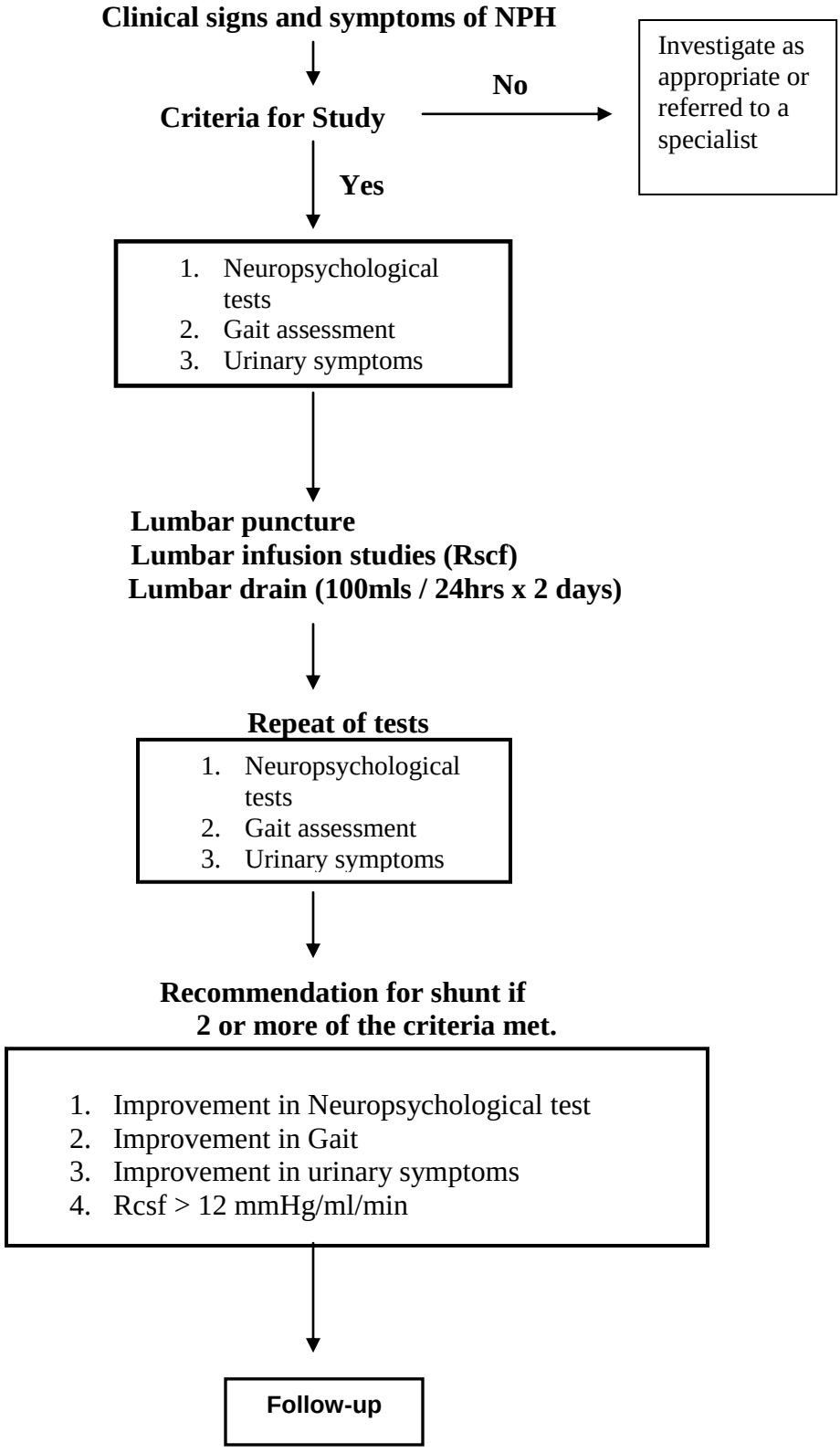
Table 3.1: Neuropsychological and gait tests used in the study.

Neuropsychological tests	**Gait tests**
Beck depression index (BDI)	10 metre walking time
National adult reading test (NART)	10 metre walking steps
Mini mental scoring examination (MMSE)	360 turn time
Verbal fluency –FAS and animal	360 turn steps
Clock drawing	

CANTAB Test	

A senior physiotherapist in the neurosurgery department conducted the gait assessment. The time taken and number of steps taken to walk 10 metre (aided or unaided) and a 360-degree turn were recorded. If patients were on anticoagulants they were stopped before a lumbar puncture was performed. Informed consent was obtained from all patients and risk explained. Subsequently, all patients underwent a lumbar puncture to measure the opening CSF pressure and a constant infusion flow study was performed to calculate the resistance to CSF (Rcsf) as discussed in section 3.7.3. Following this procedure, an external lumbar drain (ELD) was inserted for 2 days and 100mls of CSF removed every 24hours. Neuropsychological tests and gait assessments were repeated and subjective improvement in their urinary symptoms was noted. After the results were compiled, specific criteria were used to recommend a shunt operation and further discussion with the patient and family was done, explained in chapter 3.3.3. A flow chart summarising this methodology is shown in figure 3.1.

Figure 3.1. Flow chart of the study protocol.



3.3.3 Treatment selection criteria

Following the ELD the following results in patients were noted:

1. Rcsf value.
2. Scores of various neuropsychological tests following ELD.
3. Scores of various gait tests following ELD.
4. Subjective reporting of improvement in urinary symptoms by patient, carer, relatives or nursing staff following ELD.

The raw scores were used to calculate if patients improved, did not improve or worsened with each neuropsychological or gait test. Subjective statements were used to categorise the urinary symptoms. In the literature there was no clear indicator to classify the improvement scores. This may be due to the fact that this may be arbitrary. The values taken in this study to define improvement, no improvement and worsening was derived from studies related to dementia of AD (Han, Cole, Bellavance et al. 2000, O'Connor, Pollitt, Hyde et al, 1989, Spreen and Strauss. 1998) and NPH patients (Iddon, Pickard, Cross et al, 1999). The outcome scores in the gait tests were derived from studies with NPH patients (Boon, Tans, Delwel et al, 1997, Stolze, Kuhtz-Buschbeck, Drucke, et al, 2000) stroke patients (Wade, 1987) and traumatic brain injury patients (Watson, 2002). There was no consensus in the literature on the level of Rcsf above which patients should undergo shunt insertion. Because of these uncertainties 12 mmHg/ml/min was used as a positive predictor for shunt insertion. This is detailed in chapter 3.7.3.1. Table 3.2 shows how the outcomes following ELD were defined.

Table 3.2: Interpretation of the scores for all the tests

Test	Measure	Improvement	No Improvement	Worse
MMSE points	Points	>2	+2 to -2	<2
VF-FAS	Points	>4	+4 to -4	<4
VF-A	Points	>2	+2 to -2	<2
Clocks	Points	>1	+1 to -1	<1
RCSF	mmHg/ml/min	>12	10-12	<9.9
Gait-time 10	Seconds	<4	+4 to -4	>4
Gait –step10	Steps	<4	+4 to -4	>4
Gait –time360	Seconds	<2	+2 to -2	>2
Gait –step360	Steps	<2	+2 to -2	>2
Urinary	Subjective	Less/No incontinence	Same as before	Worse than before

Based on the outcome from these tests patients were classified as possible, probable and unlikely (Table 3.3). This was used both following improvement with ELD and also to measure outcome of the patients during follow-up. These criteria are based upon current practice derived from the literature in large NPH series (Vanneste, Augustijn, Tan et al, 1993, Marmarou, Bergsneider, Kling et al, 2005). The patients in the 'probable' category were shunted and the patients in the 'unlikely' category were not shunted. Those patients in the 'possible' criteria were given the option of shunting and if in doubt they were shunted. In this section these results are discussed in detail.

Table: 3.3. Classification of patients following external lumbar drain

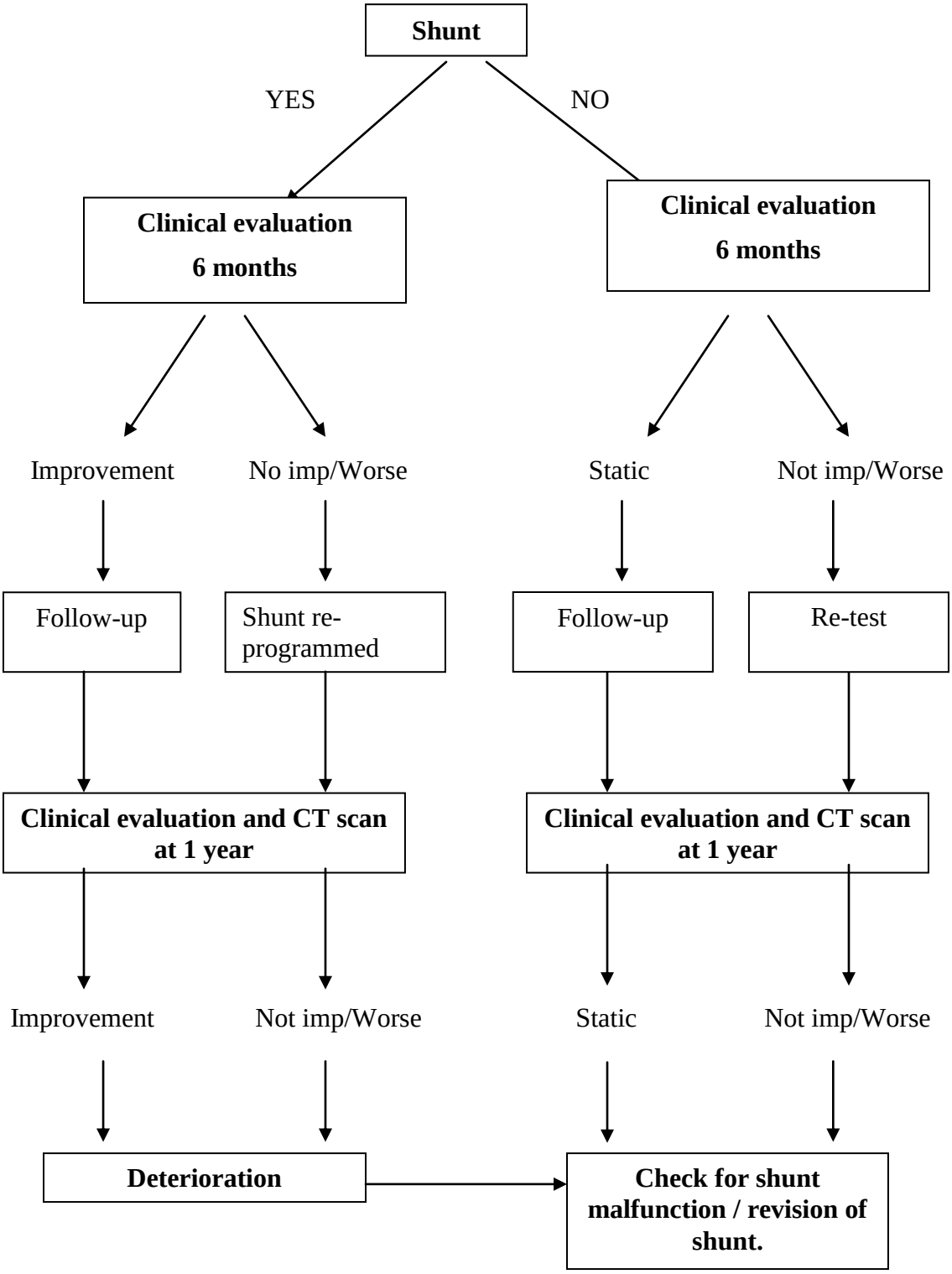
Score	Memory	Gait	Urinary	Rcsf mmHg/ml/min	Treatment
Probable	Improvement in 2 or more neuropsychological tests.	Improvement in 2 or more gait tests.	Improvement in urinary symptoms.	> 12	Shunted
Possible	Improvement in less than 2 neuropsychological tests.	Improvement in less than 2 gait tests.	No improvement in urinary symptoms.	10-12	Option to shunt
Unlikely	No improvement or worse than the baseline test.	No improvement or worse compared to baseline test.	Worse than the baseline urinary symptoms.	<10	Not shunted

3.3.4 Follow-up

All patients irrespective of the shunt placement were assessed at 6 months and 1 year. Patients who were shunted were further reviewed between four and six weeks after surgery as a routine to perform a CT scan and check for any post operative complications and wound healing. CT scans were reviewed for ventricular catheter position and subdural collections. If they had any symptoms or signs of under drainage or over drainage their shunt settings were adjusted accordingly by 10-20 mm H_20. Every time a shunt setting was changed they were reviewed in four weeks to check the effect of change. X-ray was done to check the change in the programme. CT scans were obtained at 4-6 weeks and 1 year in the shunted group and at 1 year only in the non-shunted group. The patients and their family or carers were interviewed on each follow-up. They were asked about their current symptoms and development of any new symptoms or neurological deterioration. Neuropsychological test except NART and BDI and gait tests were performed. The patients CT scans were then reviewed for a) Evans' index b) periventricular

changes and d) subdural collections or cerebral ischemia. Patients were then asked to grade their improvement in each of their three symptoms as improved, not improved and worse than before. Depending on their outcome the shunt was reset by 20-30 mm H_2O if they had no improvement or worsening in the shunted group. If they showed satisfactory improvement the shunt setting was unchanged. In the non-shunted patients if there was significant deterioration they were given the option of repeating the study. The flow chart in Figure 3.2 explains the follow up.

Figure: 3.2. Flow chart of follow-up protocol.



3.4 Neuropsychological tests

3.4.1 Introduction

In chapter 1.3 the clinical features and presentations of dementia were discussed in detail. Deficits associated with NPH tend to be mild to moderate subcortical dementia which is best differentiated from cortical dementia by the absence of aphasia, apraxia and agnosia (Boon, Tans, Delwel et a, 1997). More specifically, neuropsychological alterations associated with NPH include impaired memory and ability to manipulate acquired knowledge, deficits in visuospatial function and spatial recognition, psychomotor slowing and decreased speed in processing complex information and poor executive function (particularly on initiation and perseveration tasks) (Iddon, Pickard, Cross, et al, 1999, Thomsen, Borgesen, Bruhn, et al, 1986, Vanneste. 2000). Thus deficits are quite wide ranging indicating that a variety of neuropsychological tests should be employed, but there appears to be little consensus regarding which tests should be utilised.

3.4.2 Neuropsychological tests chosen for this study

The neuropsychological components of NPH are probably the most difficult to assess and differentiate from other forms of dementia. Dementia in NPH has traditionally been assessed using a brief screening tool such as the Mini Mental State Examination (MMSE) (Adams, Fisher, Hakim, et al.1965). This type of examination provides an overview of the cognitive functioning of patients allowing their degree of dementia to be determined, but it fails to provide details of patterns of specific impairment. A more detailed knowledge of the cognitive deficits shown by NPH patients would; (i) enable this disorder to be differentiated from dementia of the Alzheimer and other types (ii) allow assessment of cognitive improvement after surgery and (iii) may

provide some indication of those most likely to benefit from surgery. For these reasons MMSE cannot be used on its own to assess the type of neuropsychological deficit.

Table 3.4 shows some of the tests that have been used in the literature in larger series. Only a few of these tests have been used more than once. Marmarou et al, 2005, used the MMSE and a series of neuropsychological tests. The other tests were used to test attention and concentration including, digital span forward and backward tasks. The Rey auditory verbal learning test was administered as a measurement of verbal fluency skills. Golomb et al, 2000 realised that those who scored less in the neuropsychological tests had an increased gait and bladder function and were more likely to have concomitant Alzheimer's disease. Iddon et al, 1999 proposed that early detection of NPH through clinical investigation and neuropsychological assessment would increase their likelihood of improvement from a shunt. They used the computerised battery of neuropsychological tests (CANTAB) described in the following chapters. Thomsen et al, 1986, gave their sample neuropsychology grades which equated to no impairment, slight impairment, moderate impairment, severe impairment and un-testable. Although there was no significant improvement found post-operatively, for the group of patients as a whole, 73% did improve with regards to their "neuropsychological grade". The dementia caused by NPH did not completely reverse, but the patients did regain some of their abilities. The majority of tests however are designed to assess for dementia, which is subcortical. Boon et al, 1997, in the Dutch NPH study, attempted to establish particular baseline characteristics of NPH. They used a battery of psychometric tests that found NPH patients to have memory deficits, diminished visuospatial abilities, inertia and psychomotor slowing. They proposed that the dementia was a mild to moderate subcortical type. Gustafson and Hagberg, 1978, found NPH patients to have disturbances in their visuospacial abilities. Following shunt surgery only 39%

improved with regard to their cognitive ability. In contrast to the previous study, duration of illness was inversely correlated with improvement following surgery. Of those who improved, the mean duration of illness was 18.5 months in contrast to the unimproved who had a mean length of 57 months. Meir, 1999 found higher rates of improvement following shunt surgery, of 65% at short term follow-up. A mild regression was noted at long term follow-up as only 54% remained improved.

The literature review shows that NPH patients need to be assessed for information processing, memory, attention, conceptualisation and reasoning, visuospatial and constructional abilities, verbal and visual ability, remote language and executive processes. However, some of these patients may show quite severe dementia signs, many of the traditional neuropsychological tests may prove too difficult for them to complete. To avoid this problem, the MMSE is used as a short screening test, which provides information on attention, initiation/perseveration, construction, conceptualisation and memory in addition to an overall dementia. This has been widely used in most studies (Marmarou, Young, Aygok et al, 2005, Golomb, Wisoff, Miller et al, 2000, Farina, Pomati and Mariani 1999, Iddon, Pickard, Cross et al, 1999). MMSE score has reasonable reliability and validity (Salmon, Thal, Butters et al, 1990). This is discussed later in section 3.4.4.

Depressed patients often show a lack of interest or lack of motivation to complete tests. Hence, a depression-screening test, The Beck Depression Inventory (BDI) was used. BDI has not been used widely in NPH patients. There is a substantial variation in cognitive ability within populations and to compare an individual's performance with the population norm a National Adult Reading Test (NART) was used. There is impairment of both phonemic and semantic tasks associated with subcortical dementia; therefore a verbal fluency test was used to identify

this. Several studies have noted problems with visuospatial function in NPH (Thomsen, Borgesen, Bruhn et al, 1986). A quick way to assess this was by using the Clock drawing task.

Together, these tests will provide a comprehensive assessment of cognitive deficits that occur as a result of NPH. This will enable a detailed assessment of the neuropsychological effects of shunt placement and may ultimately provide more information regarding the patient clinical symptoms that are most likely to respond to surgery. Patients with NPH are easily prone to fatigue and cannot tolerate multiple and complex tests (Miyoshi, Kazui, Ogino et al, 2005). Table 3.1 summarises the tests that were used in the study, these tests are well validated and documented further.

Table 3.4: Neuropsychological tests used in the literature

Study	Tests Used / Advocated
Marmarou et al., (2005)	MMSE, Galveston Orientation and Amnesia Test, Controlled Oral Word Association Test and Benton Visual Retention Test–Revised, Digit Span Forward and Backward tasks, The Wechsler Memory Scale–Revised Logical Memory Test, The Rey Auditory Verbal, Learning Test.
Golomb et al., (2000)	MMSE, Global Deterioration Scale, Guild paragraph recall test, Digit symbol substitution test, Mefferd & Moran Perceptual Speed Test, Purdue Pegboard Test
Vanneste (2000)	Trial Making Tests B & C, Symbol Digit Memory Test, Stroop Test
Boon et al., (1999)	10 word Digit Span Forwards & Backwards, Trial Making, Finger Tapping
Farina et al., (1999)	MMSE, Digit Span Forward and Backward, Coris Block Tapping Test, Logical Memory Test, Verbal Fluency, Paired Associates Learning Test, Token Test, Rey- Osterrieth Complex Figure Copy & Recall, Revens Coloured Preogressive Matrics, Attentional Matrices
Iddon et al., (1999)	MMSE, Kendrick Objective Learning Test (KOLT), CANTAB (Visual recognition, Spacial recognition, ID/ED Attention Set Shifting Paradigm)
Larsson et al., (1991)	Bingley Memory Test, Ravens Matrices, Reaction Times, Cronholme-Molander test, 5 Item Memory Test, Identical Forms.
Thomsen et al., (1986)	Digit Span Forwards & Backwards, Ten Words Recall (>5min), Trial Making Tets A, Finger Tapping Test
Gustafson & Hagberg (1978)	Stroop Test, Reaction Time, Block Design, Word Definition Test, Paired Associates (Memory for Design & Visual Attention)

MMSE – Mini Mental State Examination, CANTAB- Cambridge Neuropsychological Test Automated Battery.

3.4.3 Screening Tests

3.4.3.1 National Adult Reading Test (NART)

The substantial variation in cognitive ability within populations can be standardised by a NART test to predict the premorbid IQ. This is important as IQ may determine performance on some tests. The NART is a UK based test which is reported to accurately estimate the IQ by asking patients to read words with non-phonetic spelling (Nelson 1982). If the IQ was very low then this had a serious impact on the scores following ELD.

Test administration:

This is simply a list of 25 words that the patient was asked to read aloud (Appendix 3). This is the short version of the test as the full version contains 50 words. The examiner kept a list of the same to score their response. Correct pronunciations were adhered to, regional accents were allowed. To score the NART, all the correct response was added together. Since the short version (25 words) was used the score was converted to the full NART score using Table 3.5. The number of errors made on the test determined the NART score. To obtain the premorbid IQ the following equation was used:

Premorbid IQ = 128 – 0.83 x NART error score.

Table 3.5: Conversion table for the prediction of the full NART Error score from the short NART score.

Short NART correct score	**Conversion to full NART Error score**
0-11	As in full NART (50 minus correct)
12	38
13	36
14	34
15	33
16	31
17	30
18	28
19	26
20	24
21+	As in full NART (50 minus correct)

3.4.3.2 Beck Depression Inventory (BDI)

Depression causes sadness, inactivity, difficulty in thinking and concentration, feelings of hopelessness, and lack of motivation to complete tests. Many severely depressed patients will have some mental deficits including poor concentration and attention. When dementia and depression are present together, intellectual deterioration may be exaggerated. Depression, whether present alone or in combination with dementia, can be reversed with proper treatment. Without this measure, it may be assumed that the patients performed poorly for other reasons

(Beck, Ward, Mendelson, et al, 1961). The BDI is a 21 item self-report rating inventory measuring characteristic attitudes and symptoms of depression. It is a widely used questionnaire to screen patients for depression. Beck et al introduced the original version of the BDI, in 1961. The BDI was revised in 1971 and has been developed in different forms including several computerized forms, a card form the 13-item short form and the more recent BDI-11 form. The reliability of internal consistency for the BDI ranges from 0.73 to 0.92 with a mean of 0.86 (Beck, Steer and Garbin. 1988). Beck suggested that if the BDI was re-administered within a short interval then scores could be spuriously inflated due to memory factors. In one series re-test reliabilities ranged from 0.48 to 0.86 (Groth-Marnat, 2nd Edition, 1990). BDI has a high content validity, and validity in differentiating between depressed and non-depressed people.

Table 3.6: Depression scores

Score	Level of depression
05 – 09	These ups and downs are considered normal
10 – 18	Mild to moderate depression
19 – 29	Moderate to severe depression
30 – 63	Severe depression

The BDI is scored by adding up the scores for each of the twenty-one questions to obtain the total score. The highest score for each of the twenty-one questions is three and the highest possible total for the whole test is sixty-three. The lowest possible score for the whole test is zero. The depression scores are interpreted as in Table 3.6.

Test administration:

The BDI takes approximately10 minutes to complete. Patients were requested to read each group of statements carefully, and then pick out the one statement in each group that best describes the way they have been feeling during the past two weeks, including the day of the test. They were not allowed to choose more than one statement for any group and if they did the highest score are taken. A sample of the questionnaire is attached in Appendix 4.

Those patients who were severely depressed were referred to a psychiatrist and treated if necessary before further tests were carried out.

3.4.4 Mini Mental State Examination (MMSE)

The MMSE is a brief, quantitative measure to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. Folstein first described MMSE in 1975 (Folstein, Folstein and McHugh. 1975) that suggested a cut-off score of 23/30 or less, for the presence of dementia in persons with at least 8 years of education. It was called "mini" because it did not test for mood and thought disorders, which are included in the full mental test. Some screening tests are unable to detect mild impairments and underestimate the level of subcortical dementia (Vanneste. 2000).

Cognitive performance measured by the MMSE varies within the population by age and educational level. The normative data for different ages and educational levels are presented in the table 3.7. The NART scores give us an approximate level of the patient's education and premorbid IQ. There is an inverse relationship between MMSE scores and age.

Table 3.7: Mini mental state examination normative data for age and education level*

	Age				
Education	**65-69**	**70-74**	**75-79**	**80-84**	**>84**
4th grade	22	22	21	20	19
8th grade	26	25	25	25	23
High school	28	27	27	25	26
College	29	28	28	27	27

* Crum, Anthony, Bassett, et al, 1993.

MMSE has been used extensively in the assessing patients with dementia. O'Connor, Pollitt, Hyde et al, 1989, found a sensitivity of 86% and a specificity of 92% when a cut-off of 23-24/30 was used. The benefits of the MMSE include its brevity (5-10 minutes to administer), and the fact that it is a global assessment of many domains including: orientation to time and place (10 points), registration of 3 words (3 points), attention and calculation (5 points), recall of three words (3 points), language (8 points) and visual construction (1 point). It is an 11-question measure that includes assessments of personal orientation, immediate and delayed memory recall, attention and calculation, language, reading writing and copying skills. The maximum score is 30. In addition, when used repeatedly the instrument is able to measure changes in cognitive status that may benefit from intervention.

The dementing range is 0-23; non-dementing range is 24-30 (Iddon, Pickard, Cross et al. 1999). A recent meta-analysis of 37 longitudinal studies where the MMSE was used to follow patients with Alzheimer Disease over a 10 year period found an average ARC (annual rate of

change score) of 3.3 MMSE points (Han, Cole, Bellavance et al, 2000). Scores range from 25-30 for normal, 21-24 for mild, 14-20 for moderate, and less than 13 in severe for patients with AD.

Studies, which have utilised such screening tests, have found patients with NPH have moderately impaired MMSE score although the specific aspects of impairment cannot be identified. Hence, it does not replace a complete clinical assessment of mental status. In addition, the instrument relies heavily on verbal response, reading and writing. Therefore, patients with hearing and visually impaired have low English literacy, or those with other communication disorders may perform poorly even when cognitively intact. Since there is a risk of underestimation of the extent of the sub cortical dementia other tests are required.

Test Administration:

The patients were asked to perform a variety of verbal, nonverbal and paper and pencil tasks in a quiet setting. During the examination the patients were given explanation more than once if they did not understand a command. Appendix 5 shows a typical MMSE form used. The total score was marked out of 30.

3.4.5 Verbal Fluency

The purpose of this test was to evaluate the spontaneous production of words beginning with a given letter or of a given class within a limited time. There are two parts to this test. The first part assesses how many words the patient can think of in one minute beginning with the letters F, A or S. Patients with frontal lobe damage (as in NPH) often have difficulty doing this and repeat the same words. The second part of the test asks participants to think of as many

objects as possible belonging to a certain category (e.g. animals). This part of the test in relatively insensitive to frontal lobe damage but is impaired in AD. Therefore this test may help to distinguish patients with Alzheimer's from those with NPH (Spreen and Strauss. 1998).

3.4.5.1 Verbal fluency - FAS

Test administration:

A stopwatch was needed and the instructions were given clearly and if necessary repeated as these patients can take longer to understand. The patient was given one minute to name as many words as possible beginning with the letters F, A and S. No proper nouns were allowed and local slang words were accepted. An example with any word was given where necessary (Appendix 6.1).

The scores were the sum of all administered words for the three letters. Slang terms and foreign words that are part of Standard English were accepted. The results were compared to those in the Table 3.8 to judge how well the patient performed at different points. For statistical calculation raw scores rather than the percentile scores were used.

Table 3.8: Percentile conversion of verbal fluency - FAS scores

	Age 60-79			Age 80-95		
	Number of words			Number of words		
Percentile	**0-8**	**9-12**	**13-21**	**0-8**	**9-12**	**13-21**
90	39	54	59	33	42	56
80	36	47	53	29	38	47
70	31	43	49	26	34	43
60	27	39	45	24	31	39
50	25	35	41	22	29	36
40	22	32	38	21	27	33
30	20	28	36	19	24	30
20	17	24	34	17	22	28
10	13	21	27	13	18	23
Mean	*25.3*	*35.6*	*42*	*22.4*	*29.8*	*37*

3.4.5.2 Verbal Fluency - Animals

Test administration:

In exactly a similar method, instructions were given to the patients for the verbal fluency animals test. Appendix 6.2 gives instructions used for the test. The scores are the sum of all administered words for animals. The results were compared to those in the Table 3.9. For statistical calculation we have used the raw scores rather than the percentile scores.

Table 3.9: Percentile conversion score for verbal fluency animal scores.

	Age 60-79			**Age 80-95**		
	Number of words			**Number of words**		
Percentile	**0-8**	**9-12**	**13-21**	**0-8**	**9-12**	**13-21**
90	20	22	25	18	19	24
70	17	19	22	16	17	20
50	14	17	19	13	14	16
30	12	14	16	11	12	14
10	11	12	13	9	11	12
Mean	*14.4*	*16.4*	*18.2*	*13.1*	*13.9*	*16.3*

3.4.6 Clock drawing

The purpose of this test is a clinical screening task for visuospatial and constructional disabilities as well as general dementia (Spreen and Strauss 1998), particularly sensitive to temperoparietal regions. The simple free-hand drawing of a clock face has been part of the brief mental status examination in neurology for a long time (Battersby, Bender, Pollack et al, 1956, Critchley, 1953, Goodglass and Kaplan. 1972). In contrast to the primarily verbal content of most dementia scales, clock drawing relies on visuospatial, constructional, as well as higher-order cognitive abilities. The test requires merely a sheet of paper and a pencil and can be given as part of a bedside examination, or in other instances when lengthy neuropsychological testing is not possible. The Clock Test (Tuokko, Hadjistavropoulos, Miller et al, 1995) uses three tasks: clock drawing (with pre drawn circles), clock reading, and clock setting.

Discriminant validity of the test has been investigated in differentiating groups of normal elderly subjects and patient groups with AD, multi-infarct dementia, and depression (Wolf-Klein, Silverstone, Levy et al, 1989), with a mean age of 76 years. Correct classification in normal subjects was 97 percent, for AD patients 87 percent, for multi-infarct dementia 62 percent, and

for depression 97 percent. Tuokko, Hadjistavropoulos, Miller et al. 1992 report a correct classification rate of 86 percent for Alzheimer's disease and of 92 percent for normal elderly controls. O'Rourke, Tuokko, Hayden et al 1997 also found good predictive validity; sensitivity was 91 percent at time of first testing for persons diagnosed with AD, and specificity was 95 percent. (Kozora and McCullum. 1994) reported a mean score of 6.61 (range 2-10) in AD patients as compared to 9.59 for normal age-matched control subjects. Libon, Wenson, Barnoski et al, 1993 found, however, that the test does not discriminate between AD and vascular dementia patients and the authors found that in a similar condition, patients with cerebrovascular dementia performed worse than patients with AD. A second study (Libon, Malaniut, Swenson et al, 1996) with a different population of 31 AD and 27 cerebrovascular dementia patients confirmed this result. While the test may be useful in the diagnosis of AD and other forms of dementia, it should be noted that this test serves many purposes. Basically, it provides an estimate of visuospatial as well as cognitive skills and hence can be altered in patients with visual pathway defects. In NPH this test is very useful in differentiating cortical from subcortical dementia.

Test administration

An unlined letter-size sheet of paper and a pencil was placed in front of the patient and the instructions are given to draw a clock face and mark 20 minutes to 4 o'clock on the clock. Instructions were repeated or rephrased if the patient did not understand, but no other help was given. The time taken to complete the task may be noted although this has not been used in this study. Pre-drawn circles were not used as part of the standard administration, but may be used if the patient fails to make a connected drawing (score of three or less according to the scoring

criteria below) in order to explore specific aspects of number placements and hand settings. Approximate time for administration was usually 5 minutes. A 10-point scoring system, adapted from Sunderland, Hill, Mellow et al, 1989 and Wolf-Klein, Silverstone, Levy et al, 1989 is was as in Table 3.10. Roman numerals are acceptable. Appendix 6.3 gives a sample instruction.

Table 3.10 Scoring of the clock drawing tests

Score	Description
10	Normal drawing, numbers and hands in approximately correct positions, hour hand distinctly different from minute hand and approaching 4 o'clock.
9	Slight errors in placement of hands (not exactly on 8 and 4, but not on one of the adjoining numbers) or one missing number on clock face.
8	More noticeable errors in placement of hour and minute hand (off by one number); number spacing shows a gap.
7	Placement of hands significantly off course (more than one number); very inappropriate spacing of numbers (e.g., all on one side)
6	Inappropriate use of clock hands (use of digital display or circling of numbers despite repeated instructions); crowding of numbers at one end of the clock or reversal of numbers.
5	Perseverated or otherwise inappropriate arrangement of numbers (e.g., numbers indicated by dots). Hands may be represented, but do not clearly point at a number.
4	Numbers absent, written outside of clock or in distorted sequence. Integrity of the clock faces missing. Hands not clearly represented or drawn outside of clock face.
3	Numbers and clock face no longer connected in the drawing. Hands not recognizably present.
2	Drawing reveals some evidence of instructions received, but representation of clock is only vague; inappropriate spatial arrangement of numbers.
1	Irrelevant, uninterruptible figure or no attempt.

3.4.7 Cambridge Neuropsychological Test Automated Battery (CANTAB)

CANTAB is a series of computerised tests completed by the patient via a touch screen on a portable computer. CANTAB has been shown to be useful in early detection of different forms of dementia. It was found to be sensitive enough to detect alterations in cognitive ability pre and post shunt in patients with NPH (Iddon, Pickard, Cross et al, 1999). In addition, this battery was also able to differentiate between patients with mild dementia of Alzheimer's type and NPH. Tests include those for reaction time, frontal lobe (executive) function, visuospatial ability & memory. An advantage of this battery of tests is that it can be administered at the patient's bedside or at home, as the system is portable. In addition all data is held on the computer and can instantly be compared to that of age matched normal subjects (Iddon, Pickard, Cross et al, 1999). In this study patients were divided into two categories dependent on whether they scored within or outside of the dementing range on the MMSE. They suggest that although these patients were able to complete the MMSE, it is not sensitive enough to detect mild dementia caused by NPH. When assessed by way of the CANTAB, these patients were found to have deficits in verbal fluency, but were not found to be significantly impaired on tasks of semantic fluency i.e. naming animals. They were impaired preoperatively in comparison to controls on tasks of intra dimentional / extra dimentional (ID/ED) attention shift. This task requires the patient to shift their attention on the basis of feedback given by the computer. It is particularly sensitive to frontal lobe damage. Spatial span and pattern recognition were found to be unimpaired. In contrast, Alzheimer's patients were impaired on pattern and spatial recognition, but were unaffected on the ID/ED attention set shifting task. Thus, incorporating these tests into a patient's initial assessment could be beneficial when attempting to make a differential diagnosis of NPH or Alzheimer's and thus provide early intervention. They suggest that early intervention

will result in early CSF drain and shunt surgery thereby preventing further deterioration of cognitive functioning.

3.5 Gait tests

3.5.1 Introduction

Gait disturbance is usually the initial sign and most important symptom. Meier, Zeilinger and Kintzel, 1999, found gait disturbance to be present in 92% of their sample who were in the early stages of NPH and present in 90% in the late stage. Boon, Tans, Delwel et al., 1997 found that of the 101 patients assessed only 68 were able to walk unassisted. They also noted that the gait in NPH was characterised by a decreased number of steps per minute and smaller foot - floor clearance. Stolze, Kuhtz-Buschbeck, Drucke et al, 2000 found that draining 30mls of CSF increased the stride lengths and walking velocity by approximately 23%. Various objective computerised analyses have also been carried out which look into gait velocity; stride length, reduced foot to floor clearance and postural dysfunction. A variety of gait assessment tools from a simple 10 metre walking test to video recorded assessment and complex gait mats have been used to look for improvement following an ELD or shunt. In a clinical setting a 10 metre walking test assesses the patients walking before and after ELD and during follow up. Patients with NPH are known to have disturbance of dynamic equilibrium, reduced stride length and festinating gait. This can be assessed by asking them to perform a 360 degree turn after completing their 10 metre walking test. In this section the two gait tests adopted in the study, and their administration is described.

3.5.2 10 metre walking test

Some methods of gait analysis are complex and difficult to use. Gait analysis laboratories are at the complex end of the spectrum in this respect. They tend to be of limited availability, require much costly and sophisticated equipment, and can be highly complicated to operate. Thus they are fairly unlikely to be used in everyday clinical practice. The ten-metre walking test is a frequently used outcome measure and provides objective means of following changes in patient function over time. In 1987 Wade et al first described and documented the specific use of a ten metre-walking test to monitor recovery of gait following stroke. In many cases, improvement (increase) in walking speed was accompanied by an improvement in functional performance (i.e. degree of help and instruction needed, and the type of walking aid required if needed). More recently still, a timed walk over six metres now forms one component of the Elderly Mobility Scale (Smith, 1994). This has become a very popular assessment tool in UK-based elderly rehabilitation. Two raters tested 28 normal subjects (14 men, 14 women) in the manner already described. This was a convenience sample of healthy volunteer undergraduate students readily available to the testers. This resulted in 84 (3 x 28) potential pairs of timed trials, of which 82 pairs were recorded (one pair by each rater). The percentage agreement between testers for this was 96.8%. Using the procedure, acceptable levels of inter-rater reliability were found, with a 95% CI for agreement of -0.38 to +0.38 seconds for normal young subjects and -0.36 to +0.49 seconds for traumatic brain injured subjects (Watson, 2002). This suggests the very good inter-rater reliability for the 10 metre walking test.

Though several studies have used 10 metres as a standard measure, specific discussion as to why this distance has been chosen is difficult to find, its practicality is understandable. Ten metres is probably the minimum functionally significant distance in the recovery of independent

walking. It is also probably a typical distance in clinical gait remediation, in terms of the free length of treatment areas and/or parallel walking bars. Ten metres is thus both a practical and meaningful distance to use.

Test administration:

The test required a standard electronic stopwatch and a 12-metre distance of free floor space. The corridor in the ward was used and had a start and finish line marked on the floor. It was found useful to identify a 'target', which is a metre or more beyond the finish line. In practice this was a chair. Subjects were asked to walk towards this target. This method was found to be effective in distracting the subjects' attention from the finish line and prevented them from decelerating as they approached it. Where necessary they were given the walking aid they normally used or the physical support of a nurse or physiotherapist not involved in scoring the test. For timing, the tester followed the subjects as they walked. This allows for observation of step-count and time, and had the added advantage that physical help was available if required. Additionally, a subjective assessment of their walking pattern and steadiness was made. No inter-rater reliability was performed for this test. The gait pattern was also noted routinely. Mostly the same physiotherapist performed the pre and post drainage walking tests although the tester varied on a few occasions, but standard instructions were given

3.5.3. 360 degree turn test

The 360-degree test was a good measure of the patient's posture and balance as this can be affected in NPH patients. The patients were asked to make a full turn back after they completed walking 10 metres without using any support if possible. The same physiotherapist

performed the tests and most often they demonstrated the procedure before administering. During the test the time taken to make the turn and the number of foot steps used were calculated.

3.6. Subjective analysis of urinary symptoms

3.6.1. Introduction

Urinary symptoms tend to occur at the later stages of this condition. Several methods of quantitative analysis of improved urinary function have been mentioned, which include urodynamic studies of bladder function and special scanning techniques that require specialist expertise. Such methods have not been used in this study but subjective improvement in symptoms was identified.

3.6.2 Subjective reporting

The family and or nursing staff were asked to report any improvement of urinary symptoms before and after the lumbar drain. It was a subjective score of improvement. The symptoms were graded as ‘worse’ than before, ‘no improvement’ or ‘improved’. The urinary symptoms were recorded from the time of admission to discharge. The same method was used during follow-up reviews.

3.7 CSF hydrodynamic

3.7.1 Introduction

Stasis and absorption of cerebrospinal fluid is disturbed in NPH. Tests revolved around temporary CSF drainage and dynamic measurements of CSF circulation have been the main stay of investigation in these patients since the 1960s. The most widely used methods involve a standardised CSF “tap test” introduced by Wikkelso, Andersson, Blamstrand et al, 1982 and

1986, although the first report of a tap test was by Adams et al, 1965 in their first paper describing the condition. The test involves removing large volumes of CSF (40-50 mls) by a lumbar puncture. A 40ml tap on 49 patients showed 26% sensitivity and 100% specificity (Walechenbach, Geiger, Thomeer et al, 2002). Thirty-five patients with iNPH showed a 33% specificity to tap test in another series (Malm, Kristensen, Karlsson et al, 1995). Both of these studies provide evidence to suggest that NPH patients cannot be excluded from shunting based on negative tap test. Other tests involve evaluation of CSF resistance to outflow based upon the original lumbar infusion test described by Katzman and Hussey in 1970 and Hussey, Schanzer and Katzman in 1970. Many investigators have used measurement of the resistance to outflow of cerebrospinal fluid (Rcsf) in selecting patients for shunt placement. There are different dynamic testing techniques described, including perfusion study, infusion test, bolus testing and constant infusion testing. The constant flow lumbar infusion test was used in the study to calculate the Rcsf followed by insertion of a lumbar drain to remove 100mls of CSF over 24 hours for 2 consecutive days.

3.7.2 Lumbar infusion study

The resistance to CSF absorption by the arachnoid villi can be measured and helps to predict shunt response. The lumbar infusion study was performed using a modification of Ekstedt's constant-pressure infusion technique (Ekstedt, 1978). The patients were placed in a left lateral position. Under aseptic conditions and local anaesthetic cover, a 16 G epidural needle was inserted into the thecal sac at the level of L3/L4 or L4/5. A 3-way tap was then connected and a pressure transducer was calibrated to atmospheric pressure at the level of the spinous processes of the vertebrae. The pressure transducer was connected to a monitor and opening pressure was measured after a 3-5 minute latent period before any CSF was lost. An infusion pump with

50mls of sterile 0.9% normal saline set at an infusion rate of 1.5mls/min was connected to the 3-way tap. Saline was infused through the 3-way tap from the infusion pump, till a constant plateau pressure was obtained or a pressure of 50 mm Hg was reached. The pressure change was plotted on a graph manually. The advantages of this technique are that it is simple, quick, reliable and reproducible with a low risk of complications despite being an invasive technique.

3.7.3 Rcsf

3.7.3.1 Rcsf value used to measure outcome

The infusion method of measuring the Rcsf in young volunteers showed the upper limit of normal was 10 mmHg/ml/min, with mean values of 9 mmHg/ml/min (Boon, Tans, Delwel et al, 1997). The observed range of Rcsf correlated with good outcomes range from 10 to 24 mmHg/ml/min. Various investigators have used 8 (Børgesen and Gjerris, 1982), 10 (Ekstedt, 1978. Graff-Radford, Godersky, Jones et al, 1989), 12 (Delwel, de Jong, Avezaat et al, 1989), 13 (Tans and Poortvliet, 1985) and 15 (Price, 1989) mm Hg/ml/min as a threshold. If all the patients recieved a shunt irrespective of the Rcsf value, then it might be possible to predict the threshold level accurately. However this is not feasible for reasons discussed elsewhere. Using 12.5mmHg/ml/min as a cut off value, Borgesen and Gjerris 1982, reported a positive predictive value of 84% and a negative predictive value of 100%. These good results are due to the fact that those with an Rcsf of less than 8.3 were not shunted. Although most authors have predicted measurement of Rcsf values as a positive predictor of shunt surgery some have found it not as reliable and others have found measuring Rcsf not useful in the selection of patients for a shunt (Boon, Tans, Delwel et al, 1997). A large prospective series from the Dutch group showed higher positive predictive values when the cutoff for the Rcsf was more than 18 mmHg/ml/min. Price, 1989, showed with a increasing Rcsf there was a increase in the number of patients who

improved following a shunt surgery. There is no consensus in the literature on the level of Rcsf above which patients should undergo shunt insertion. Because of these uncertainties an Rcsf of 12 mmHg/ml/min has been used as a positive predictor for shunt insertion as values 12 and greater has consistently showed a better response to shunt surgery. Patients with lower Rcsf were also shunted if they showed improvement in other criteria as discussed in chapter 3.3.3.

3.7.3.2 Calculation of Rcsf

During the study the CSF opening pressure at rest was measured at the beginning before infusion. The opening pressure in iNPH is normally between 3-18 mmHg. Lumbar pressure reading at every minute was plotted on a graph with the X-axis pressure and time on the Y-axis. The test was stopped if the patient developed symptoms of raised intracranial pressure or the plateau pressure reached 50 mm Hg or after 45 minutes of infusion. The resistance (Rcsf) to CSF absorption can be calculated using an Ohm's Law analogy:

Rcsf = Pp-Po/1.5 mmHg/ml/min

Pp – Plateau pressure

Po – Opening pressure

1.5ml/min – rate of infusion of saline.

The Rcsf in normal individuals ranges from 6 to 10 mm Hg/ml/min. It increases in the elderly.

3.7.4 External Lumbar Drain (ELD)

After the infusion study an epidural catheter was inserted into the lumbar space and secured with tapes and connect to a bag via a 3-way tap. The patients were kept in bed rest for most of the 48 hour period of CSF collection, but were allowed to mobilise to the toilet and sit up for meals after which the 3-way tap was closed. CSF was drained only in lying or semi-sitting

position. 100mls of CSF was drained every 24 hours and after 48 hours the drain was removed. Patients were encouraged to drink plenty of fluids and keep well hydrated during the drainage. The ELD was then removed at 48 hours time and within two hours the neuropsychological and gait tests were repeated.

3.7.5 Cerebrospinal Fluid Collection

The patients were asked to remain in lying position on bed most of time allowing for brief breaks for meal and toilet use. They were instructed to call for nursing help to move out of bed. In this way, we could ensure that the valve was closed to drainage when the patient was upright. At the end of two days when the required amount of CSF was collected the tests were repeated within two hours after the drain was removed.

3.7.6. Shunting criteria

After all the tests were repeated the outcome of ELD was discussed with the patients and their family and carers. This was discussed in section 3.3.3.

3.8 Treatment

3.8.1 Introduction

There is less scientific evidence on the appropriate surgical management compared to the diagnostic phase of the NPH. Although we have used specific criteria based on response to CSF drainage, when offering surgery to patients other factors such as co-morbidity and coagulation status are taken into consideration for individual patients. There is insufficient data on patients managed conservatively and the natural history of the disease. There are no published reports demonstrating returning to normality without surgery or progression if left untreated (Bergsneider, Black, Klinge et al, 2005)

Any form of CSF diversion procedure in this group of patients comes with significant risks that may be directly related to the surgery and postoperative complication. This was explained to patients and relatives before informed consent was obtained. The expectations of the patient and the family was considered and discussed in detail although there were several grey areas that could not be answered appropriately e.g., measure of improvement expected and sustained if there was improvement. In this section the co-morbid factors which influence surgical option of CSF diversion, the selection of type of shunt and the associated complications of shunt surgery have been discussed briefly.

3.8.2 Surgical management

3.8.2.1 CSF diversion procedures

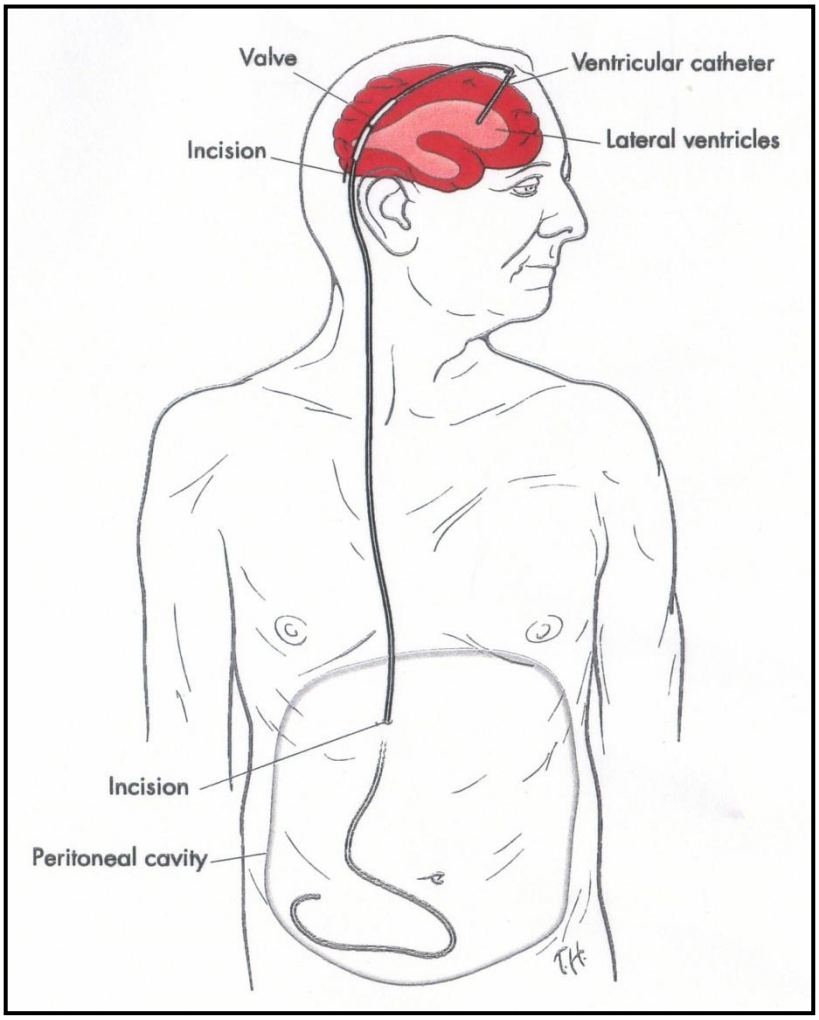
The most common method of permanent CSF diversion is a shunt. The shunt is a device that channels CSF from the ventricle to a distant site usually the peritoneum called Ventriculo-Peritoneal Shunt (VPS) Figure 3.3. Other sites used in NPH are the right atrium of the heart (ventriculo-atrial shunt or VA shunt) or pleura (ventriculo-pleural shunt) when there is a contraindication for a VPS, although VA shunts have been used extensively in some series. Another type of shunt is a Lumbo-peritoneal shunt (LP shunt), which is CSF diversion, from the lumbar CSF space to the peritoneum and these are more prone to blockage and hence not popular in NPH. It is important to realise that each of these shunt procedures have potential advantages and disadvantages. Endoscopic third ventriculostomy (ETV) has been performed for people with iNPH and aqueductal stenosis. This is performed by passing an endoscope into the lateral ventricle and perforating the floor of the third ventricle, thus diverting the CSF from the ventricle into the basal cisterns. It has proven efficacy in iNPH patients with aqueductal narrowing on

MRI flow scans (Meier, Zeilinger, Schonherr B et al, 2000. Mitchell and Mathew, 1999) but has failed to show success in patients with communicating NPH (Longatti, Fiorindi, Martinuzzi et al, 2004). In elderly population this method of treatment may have better compliance but in communicating iNPH shunts are still the preferred option. Further studies comparing the two treatment modalities may provide a definitive answer.

3.8.2.2 Ventriculo-Peritoneal Shunt (VPS)

The VPS is performed under a general anaesthetic. A burr hole is performed in the skull and the shunt tubing is tunnelled underneath the skin from the head and placed into the peritoneal cavity as shown in Figure 3.3. The shunt valve is the critical component of the shunt system. The design that has been used the longest is a fixed differential pressure valve which opens if the fluid pressure at the inlet of the valve exceeds the pressure at the outlet by a certain pressure. Traditionally, these come in low, medium and high pressure, each representing a fixed opening pressure. Most valves work with a ball and cone mechanism but other types are also available (figure 3.4). An anitisiphon device is inserted at the end of the valve to prevent the siphoning effect of gravity when the patient sits or stands. The operation was carried out usually within a few weeks after their initial admission or occasionally during the same admission.

Figure 3.3: Ventriculo-Peritoneal shunt position. (www.lifenph.com/about.asp. Webpage accessed on 20.10.2007)

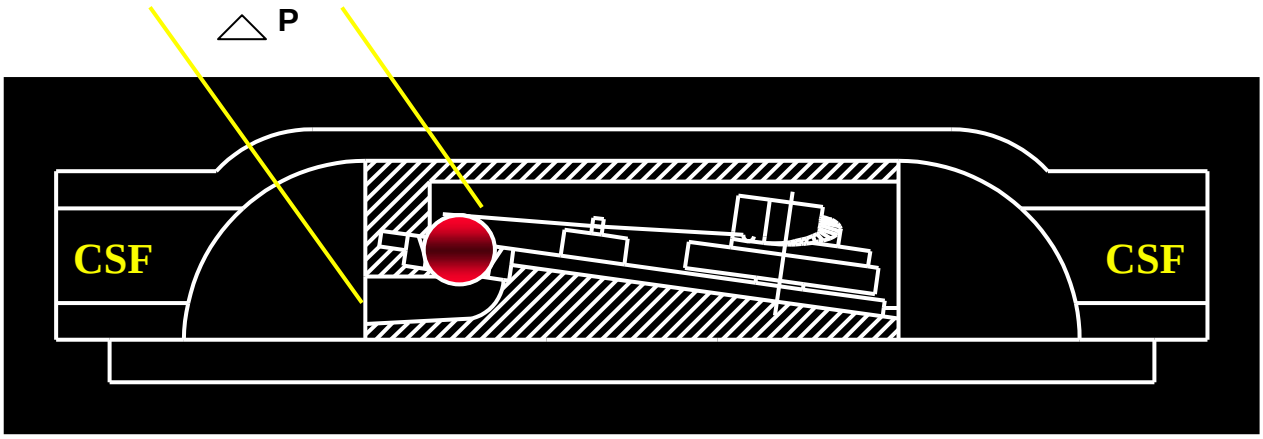


3.8.2.3 Adjustable Valves

In most large studies medium-pressure shunts were used and others used low-pressure (McQuarrie, Saint-Louis, Scherer, 1984) or high-pressure (Larsson, Jensen, Bilting et al, 1992. Benzel, Pelletier, Levy et al, 1990) valves. Vanneste, Augustijn, Dirven et al, 1992, did not find any differences between the various working pressures. The Dutch study randomized low and medium pressure valves and found low pressure with better outcomes but no statistical significance.

A CSF shunt valve with an adjustable opening pressure level was originally proposed in 1973 by Hakim. A differential pressure valve opens and begins to drain CSF at a certain pressure. Figure 3.4 shows the ball and cone mechanism of the shunt with the differential pressure across the two chambers. Because of the uncertainty of having to assume the optimal opening pressure in NPH patients (Boon, Tans, Delwel et al, 1998) adjustable valves have been used. These valves allow non invasive method of changing the pressure settings after implantation. Most of the existing literature on adjustable valves is in favour with benefit to patient's clinical outcomes (Black, Hakim, Bailey et al, 1994. Carmel, Albright, Adelson et al, 1999. Mori, 2001. Zemack and Romner, 2000 and Goran Zemack, Bertil Romne et al, 2002). Although catheter-related complications and shunt-related infections are the major causes of shunt failure, adjustable valves are very useful in managing over drainage and under drainage problems in accordance with clinical or radiological findings in the postoperative period. After procedure the subdural haematoma is a major cause of morbidity and mortality in NPH patients. This complication requires surgical treatment of the collection by burr hole drainage and ligation of the shunt or revision to a higher-pressure valve to prevent further accumulation of blood. This suggests that use of programmable valves potentially makes revision operations unnecessary.

Figure 3.4: Ball and cone valve mechanism of shunt. (With permission from Codman, Johnson and Johnson)



CODMAN® HAKIM™ Programmable Valve (CHPV) was used in this study. CHPV is the same size as a fixed differential pressure valve and is implanted in exactly the same way. It gives the added choice of 18 different programmable pressure settings (30 mm H2O and 200 mm H2O) using a programming device. The opening pressure of the valve is changed through the use of an externally applied, codified magnetic field (Fig 3.5a). The spring in the ball-spring mechanism of the valve sits on top a rotating spiral cam which contains a stepper motor (Fig 3.5b). Applying a specific magnetic field to the stepper motor will cause the cam to turn slightly, increasing or decreasing the tension on the spring, and changing the opening pressure of the valve (Fig 3.5c).

Figure 3.5 (a-c): Programmable shunt components. (With permission from Codman, Johnson and Johnson)

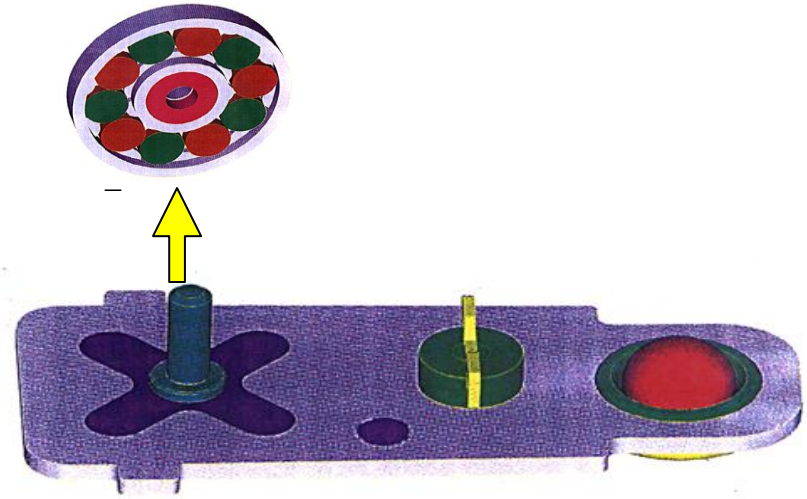


Figure 3.5a

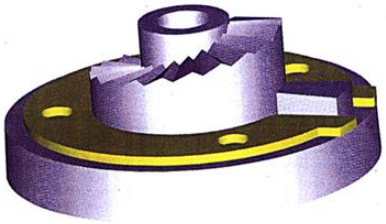


Figure 3.5b

Figure 3.5c

The following figure shows the ball and cone mechanism of the shunt. Figure 3.6 shows the red ruby ball, which is closed, and in Figure 3.7 the ruby ball lifts up when the intracranial pressure exceeds the opening pressure of the programmable valve to allow the flow of CSF.

Figure 3.6: Lateral view of a programmable shunt. (With permission from Codman, Johnson and Johnson)

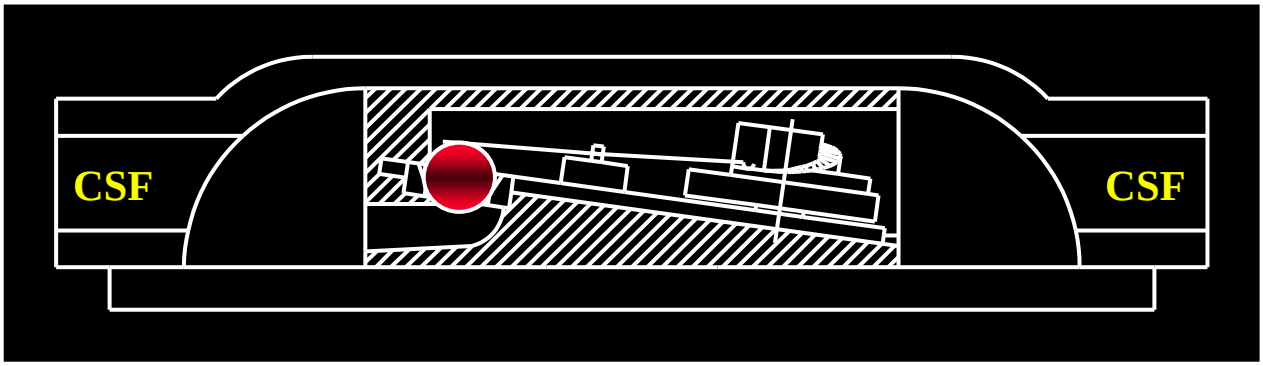


Figure 3.7: CSF flow through the valve. (With permission for Codman, Johnson and Johnson)

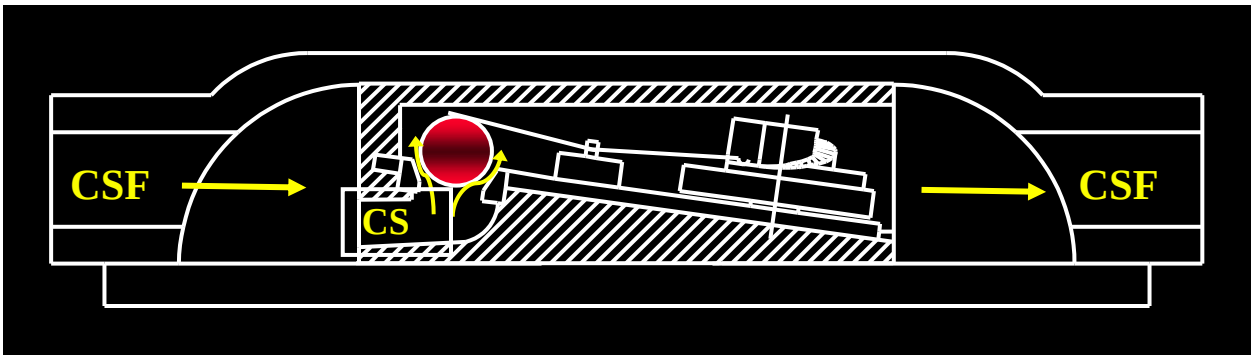
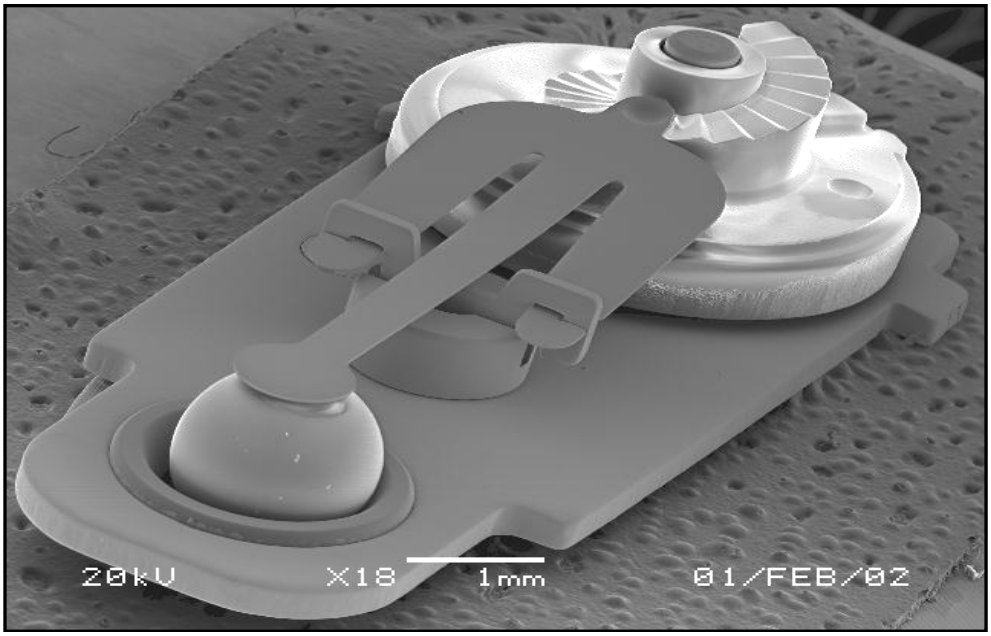


Figure 3.8: Photograph of a programmable valve. (With permission from Codman, Johnson and Johnson)



3.8.2.4. Valve adjustment strategies.

In the initial part of the study the opening pressure of the valve was set at the opening pressure during a lumbar puncture. Table 3.11 shows the corresponding pressure at which they were set. The valve pressure was adjusted when a) clinical symptoms worsened b) subdural hygromas or haematomas that could be managed conservatively developed and c) following an MRI scan when the magnetic field alters the settings. In the later part of the study the opening pressure of the valve was placed high at 130mm H_2O and gradually reduced by 20-30mm H_2O until clinical improvement was seen.

Table 3.11: Opening pressure and corresponding initial valve pressure setting.

Opening pressure at LP mm Hg	Conversion to mm H O	Opening pressure of the valve.
3	40	60 mm H_2O
4	54	
5	68	
6	81	90 mm H_2O
7	95	
8	109	
9	122	120 mm H2O
10	136	
11	150	
12	163	140mm H_20
13	177	
14	190	
15	204	140mm H_20
16	218	
17	231	

3.9 Outcome measurement

All patients, irrespective of their treatment outcome, were followed up until 1 year. The outcome measurements were kept standard throughout this study during follow-up at 6 months and 1 year. These measurements were 2 fold to assess the clinical and radiological outcomes. Firstly the outcome of the neuropsychological and gait tests along with improvement in the urinary symptoms at 6 months and 1 year, and secondly the changes on CT scans in the shunted and non-shunted patients at 1 year. During the visit at 6 months and 1 year patients were subjected to a full physical neurological examination to rule out any deficits. Chapter 3.3.4 explains in detail the follow-up of patients after treatment. The reason the same neuropsychological and gait tests were used was to report a consistency in outcome over time and to look for a change. This proved useful to detect those who improved following shunting.

Unfortunately no specific standard NPH outcome measures or general quality of life measures were used. The disadvantages of this are described more in detail is the discussion chapter 5.11.

The outcome was measured quantitatively as described in Table 3.2. The patients were classified into 3 groups improved, not improved and worse based on their scores. This classification was useful to measure the outcome over a period of time and to consider any intervention ie. Shunt adjustment or re-test depending on the results.

3.10 Statistical analysis

All data used in this study were ordinal (categorical) or continuous. Examples of ordinal data are the results of MMSE testing and categories of patients based on probable, possible and unlikely. Examples of continuous data are age and the results of 10 metre walking tests. All descriptive statistics were analyzed and summarized using commercially available software for Windows (SPSS, version 14 and higher; SPSS, Inc., Chicago, IL). The mean (M) and standard deviation (SD) was used to summarize the variables. The level of statistical significance of differences was $p < 0.05$.

Parametric data involving differences between the means of two independent samples were analyzed with the aid of the Student paired t-test. Where there were non-parametric comparisons (because of skewed distributions or small group size) between two independent groups a Mann Whitney U test was used. This was used for assessing whether two independent samples of observations came from the same distribution. The baselines characteristics of the shunted and non-shunted patients were analysed using this method.

To determine whether a linear relationship existed between quantitative variables, the Pearson rank correlation coefficient was applied to normally distributed variables. The linear association between the neuropsychological and gait tests were assessed using this.

Likelihood ratio shows us how much we should shift our suspicion for a particular test result. This was used in assessing the usefulness of the Rcsf values for selecting patients for shunting. Others tests in assessing the Rcsf value significance were the pre-test odd which shows that the patient has the target disorder before the test was carried out. Post test odds shows that the patient has the target disease after the test was carried out. The post-test probability shows the proportion of patients with that particular test result who have the target disorder.

To examine the effects of shunting and to determine whether the symptoms of NPH improve following surgery, a two way mixed analysis of variance (ANOVA) was conducted with treatment (shunt, no shunt) and post shunt assessment (six months, one year) as factors for each of the measures taken. To examine the characteristics of patients who have improved from shunt surgery, with those who showed little improvement, a two way mixed analysis of variance (ANOVA) was conducted with surgery (Improved, not-improved) and post shunt assessment (six months, one year) as factors. Differences between groups may assist in developing criteria, in the future, to select patients who are most likely to benefit from surgery. To investigate if any of the tests are able to predict surgical success or failure from the baseline tests a multiple regression analysis at one year was performed.

3.11 Ethical approval *(Ref: 2003.1.x)*

Ethics commitee approval for this research was submitted on the 30th January 2003 to the Preston, Choley and South Ribble Local Research Ethics Committee (LREC), Trust Headquarters, Chorley and South Ribble District General Hospital, Chorley, PR7 1PP and the Research and Development Directorate, Lancashire Teaching Hospital, NHS trust. Details of the protocol, patient information leaflet and consent forms were produced.

The committee had raised several questions regarding the appropriateness of the research title, sample size, statistical design, consent forms modification and finally regarding the research degree that I had submitted for. A letter and a personal representation in the LREC meeting clarified these questions.

Since most of the patients in this group were elderly and suffered from dementia the consent form was modified to include the signature of the next of kin before any research was carried out. In order to make this process more effective patients and their carers were sent information leaflets even before they were seen in the hospital and it was an absolute requirement for a carer, member of family or next of kin to attend with the patient during the first visit on the advice of the committee.

The information sheet was modified twice on the advice of the committee. The first three pages of the consent described the details about the condition, how to treat NPH and why patients required further investigation. The last page of the consent form described specifically about the various tests used in the study and how these tests would be performed. Care was taken to make it simple and in lay terms (Appendix 1).

A report from the hospital statistician and the supervisor from the University of Central Lancashire (UCLAN) were requested to discuss the sample size, statistical methods and analysis of outcome. The supervising consultant at the Lancashire teaching hospital was also consulted. The initial funding requirement was to purchase a computer called the Cambridge Neuropsychological Test Automated Battery (CANTAB) to perform the Neuropsychological tests. A report from the funding body, The Sydney Driscoll foundation, was requested.

The modified aims, methods, statistical analysis, patient information leaflet and consent were resubmitted. After several communications with the LREC and the research and development directorate the ethics committee approval was granted on the 8th April 2003. There were several conditions applied and part of this was to submit a 3000-word progress report at the end of year one. This was submitted and reviewed by 2 independent observers at the hospital and university. This was a requirement to proceed with the research and it was met. A final report was submitted to the research and development directorate at the hospital shortly after submitting this thesis. A copy of the ethics approval letter **(Ref: 2003.1.x)** is attached in the appendix.

Chapter 4: Results

4.1 Introduction

In this chapter each aim of the study is considered. Results are presented and summarised.

4.2 Demographics and clinical presentation

4.2.1 Aim 1

To compare the demographic and clinical characteristics of patients who were selected for shunting with those who were not. This may provide clearer criteria to distinguish patients suffering from NPH from those who may be suffering from other disorders with similar presentation and evaluate the outcome between the shunted and non-shunted patients.

4.2.2 Results

4.2.2.1 Inclusion and Exclusion criteria

The total numbers of patients referred to the study were 44 of which 40 met our research criteria as mentioned in chapter 3.3.1. Four patients who were excluded from the study are described in Table 4.1.

Table 4.1: Patients excluded from the study

Age	Presentation	Reason for exclusion	Action
57	Memory and urinary incontinence	Severe dementia MMSE <10. Significant cerebral atrophy for age. Possible Huntington's disease.	Referred to Neurologist for further investigation.
62	Gait problems only. On examination had cervical myelopathic.	Ventriculomegaly and MRI cervical spine showed significant stenosis with myelomalacia changes.	Had posterior cervical decompression with some improvement in gait symptoms.
78	Memory, gait and urinary symptoms.	Refused investigation and surgery.	No follow-up.
81	Memory and some gait problems.	Severe dementia MMSE<10. Possible Alzheimer's.	Referred to neurologist and started on treatment for AD.

4.2.2.2 Age

The total number of patients included in the study was 40, with an age range from 45-89 years. The mean age of the sample was 76.4 years (SD=7.47). There was one male patient aged 45 years and the mean age was similar even when this patient was excluded. Six patients were below the age of 65 years with a mean age of 57.8 years, 85% were above. iNPH patients generally present above the age of 65 years and the majority of those below this age are thought to have a secondary cause (sNPH). Table 4.7 shows the age and etiology of the patients with NPH. The 34 (85%) patients with idiopathic NPH had a mean age at presentation of 75.6 years (SD=7.7) and six (15%) with sNPH with a mean age of 71.6 years (SD=16.2).

4.2.2.3 Gender

Of the 40 patients 15 (37.5%) were male and 25 (62.5%) were female with a mean age of 76.5 and 74.76 years respectively. This is shown in Table 4.2 below.

Table 4.2: Gender and age range of all patients

Gender	Age in years		
	Minimum	Maximum	Mean (SD)
Male (N=15) (37.5%)	45	84	76.27 (9.72)
Female (N=25) (62.5%)	58	89	74.28 (8.45)

The age range and gender of the patients who were shunted and not shunted are described in the table 4.4. In the shunted patients 44% were male and 56% were female and in the non-shunted group, 35% were male and 65% were females. The mean ages between the two groups were similar. There was no difference in age between the shunted and the non-shunted groups or males and females. There were more female patients in both iNPH and sNPH groups (Table 4.3).

Table 4.3: Age range of the shunted and non-shunted patients

Gender		Shunted (N=23)	Non-Shunted (N=17)
Male N=15	N	9	6
	Mean age	77.33	74.67
Female N=25	N	14	11
	Mean age	73.86	74.82

N = count

4.2.2.4 Etiology

Of the 40 patients in the study 34 (85%) had primary or idiopathic NPH (iNPH) and 6 (15%) had secondary NPH (sNPH). Table 4.6 and 4.7 show the two groups of patients.

Table 4.4: Etiology, gender and age of patients

Type of NPH	No. of Patients (Percentage)	Male : Female ratio	Mean age in years (SD)	Age range years
Idiopathic	34 (85%)	13 : 21	75.6 (7.7)	58-89
Secondary	6 (15%)	2 : 4	71.6 (16.2)	45-84
Total	40 (100%)	15 : 25	75.6 (8.9)	45-89

Table 4.5 Etiology of the shunted and non-shunted patients

Treatment groups		Shunted Male : Female ratio	Non-Shunted Male : Female ratio
Total	N = 40	9 : 14	6 : 11
Idiopathic	N = 34	9 : 12	4 : 9
Secondary	N = 6	0 : 2	2 : 2

The mean ages between the two groups were not statistically significant although the secondary NPH patients were slightly younger (71.6 years compared to 75.6 years). Of the six sNPH patients four of them had previous cranial surgery and only two were shunted. More details of the patients are shown in Table 4.8.

Table 4.6: Details of secondary NPH patients

Age	Cause	Treatment	Latent Period
45	Right parietal AVM	Craniotomy for excision of AVM	18 year
58	Head Injury	9 weeks coma, conservative treatment	12 years
80	SAH	Conservative management	Approx 10 years
81	Meningioma	Craniotomy and excision of tumour	4 years
82	SAH	Craniotomy for MCA aneurysm clipping	8 years
84	SAH	Craniotomy for AComA aneurysm clipping	24 years

AVM – Arterio-venous malformation, SAH – Subarachnoid haemorrhage,
MCA – Middle cerebral artery, ACom A – Anterior communicating artery.

4.2.2.5 Clinical symptoms

During presentation the triad of gait, memory and urinary symptoms was present in 32 patients (80%) with gait being the first symptom in 34 patients (85%). Memory occurred as the second most common symptom in at least 57% of the patients and urinary problems as the final symptom to be noticed in 13 patients (32%). Eight patients (20%) noticed all three symptoms of the triad to have started around the same time. Gait and memory symptoms were present in 38 patients (95%), gait and urinary symptoms in 34 patients (85%) and memory and urinary symptoms in 32 patients (80%) of the total. These results are summarised in Table 4.7 and 4.8. Gait was the predominant symptom in all patients, memory and urinary symptoms in 95% and 85% of patients respectively. Urinary symptoms were not present in 15% of patients.

Table 4.7: Frequency of NPH symptoms.

Symptoms in months	Number of patients	Percentage
Triad – gait, memory and urinary.	32	80%
Gait and memory	38	95%
Gait and urinary	34	85%
Memory and urinary	32	80%

Patient's duration of symptoms at presentation were compared between those shunted and not shunted. Twenty-three patients (57.5%) were shunted and 17 (42.5%) were not shunted in this study. No difference was found in the duration of symptoms between the shunted and the non-shunted patients in their memory and urinary symptoms but a marginally not statistically significant difference for gait with the shunted group having the longer duration of symptoms was noted (Table 4.8). This could partly be due to the fact that three patients had gait problems for more than five years while the others had a mean of 21.4 and 15.7 months of symptom duration in the shunted and non-shunted groups respectively.

Table 4.8: Details of the symptoms characteristics in the shunted and non-shunted patients

		Total Mean (SD)	Shunted Mean (SD)	Non-Shunted Mean (SD)	p values
N		40	23	17	
Gender		Male = 15 Female = 25	Male = 9 Female = 14	Male = 6 Females = 11	
Symptoms in months means(SD)	Gait	22.68 (16.3)	25.9 (17.53)	17.25 (13.35)	0.076
	Memory	15.20 (11.23)	15.8 (12.23)	14.56 (10.37)	0.354
	Urinary	7.29 (7.84)	6.1 (8.28)	9 (7.35)	0.147

The mean duration of symptoms was 22.68 months for gait, 15.20 months for memory and 7 months for urinary symptoms. In the shunted group, 78% of the patients showed

improvement in memory, 83% of the patients showed improvement in their gait and 26% of the patients improved in their urinary symptoms at 1 year. Table 4.9 shows the outcome of shunted patients in percentage.

Table 4.9: Outcome of shunted patients

		Outcome at 6 months		Outcome at 1 year	
Count	Symptoms	Improved	Not Improved	Improved	Not Improved
Shunted Patients (23)	Memory	39%	61%	78%	22%
	Gait	52%	48%	83%	17%
	Urinary	39%	61%	26%	74%
Overall		43%	57%	74%	26%

Of those patients who had the triad of symptoms 70% showed improvement at 1 year and 30% did not show any improvement. Patients presenting with only two symptoms showed a higher percentage (83%) of improvement compared to the patients having the classical triad (Table 4.10).

Table 4.10: Symptoms and outcome of shunted patients at 1 year

	Improved	Not improved	Total
Triad present	12 (70%)	5 (30%)	17
Only 2 symptoms	5 (83%)	1 (17%)	6

4.2.2.6 Co-morbidity

Co-morbidity plays a significant role when making a decision to offer shunt surgery and patients with significant cerebrovascular disease respond poorly to shunt placement. Table 4.11 shows a detailed analysis of the co-morbid factors in the shunted and non-shunted groups. These factors are represented as events and some of these events can be present in the same patient. There was no difference in the co-morbid risk factors between the two groups of patients.

Table 4.11: Co-morbidity of NPH patients.

Co-morbidity	Shunted group	Non-Shunted group
Cerebrovascular disease	5	4
Hypertension	7	8
Ischemic heart disease	4	4
Myocardial infarction/IHD	3	2
Diabetes Mellitus	2	1
Prostate symptoms	2	1
Depression	2	4
Osteoporosis/osteoarthritis	2	2
Hypercholesterolemia	1	2

IHD – Ischemic Heart disease

4.2.3 Summary

Age, gender, etiology and marginally duration of symptoms were not associated with any difference in the outcome between the shunted and the non-shunted patients. It was not possible

to predict the outcome of the shunted patients based on their clinical presentation. Co-morbidity did not influence the selection or outcome of shunting.

4.3 Radiology Evaluation

4.3.1 Introduction

CT scans not only help in diagnosing and differentiating NPH from other conditions; it is also used to evaluate the prognosis of the condition following treatment. In the shunted patients CT scans were performed at intervals to identify the position of the shunt catheter, assess the size of the ventricles and detect postoperative complications like subdural collections. In the non-shunted patients CT scans help as a prognosticator of the disease process. Section 1.4.2 explains the CT scan characteristics used in differentiating other conditions and various measurements that can be used to evaluate the size of the ventricles following a shunt. The prognostic value of a CT scan on its own is limited.

4.3.2 Aim 2

To evaluate the usefulness of the CT scan in identifying and preventing complications and predicting outcome at one year between the shunted and the non-shunted patients.

4.3.3 Results

Ventriculomegaly was determined based on an Evans' index equal to or greater than 0.30. Other parameters that were noted are CT scan evidence of previous cerebral infarcts and peri-ventricular lucency. The Evans' index is defined as the maximal width of the frontal horns measured at their extreme to the maximal biparietal diameter (figure 1.2). In the shunted patients scans were performed 4-6 weeks after their operation to identify any complications. After this

they had a further scan at one year. The non-shunted patients had only one scan at the one-year follow-up.

A reduction in the Evans' index of more than 0.12 was defined as a clear or significant reduction in the ventricular volume, whereas a reduction of at least 0.06 to 0.11 was classified as a moderate improvement and a differential of 0.05 was regarded as no reduction in ventricular volume.

Evans' index scores: 0.00 – 0.05 = No reduction in ventricular volume
0.06 – 0.11 = Moderate reduction in ventricular size
0.12 – 0.18 = Significant reduction in ventricular size

4.3.3.1. Baseline radiological findings

The baseline radiological variables noted were Evans' index, periventricular edema and evidence of cerebral infarcts. The mean Evans' index of all patients was 0.43 (SD = 0.097). The mean of the shunted patients was 0.422 (SD = 0.077) and the non-shunted patients were 0.443 (SD = 0.120). There was no significant difference between the groups in the baseline Evans' index. Nine (22.5%) patients showed periventricular changes on the CT scan and six (15%) patients showed evidence of previous infarcts. Of the nine patients with periventricular changes five were shunted and only two out of six patients with previous infarcts were shunted. These patients were reviewed at a one-year scan for changes.

4.3.3.2. Radiology finding at 4-6 weeks

The CT scans performed at 4-6 weeks were to rule out shunt related complications like subdural hygromas or haematomas and mal-position of the ventricular catheter. The Evans' index was not reviewed at 4-6 weeks. Three patients developed a subdural hygroma on CT which

was managed conservatively and two other patients developed subdural haematoma, one of them requiring surgery for evacuation of the haematoma. One patient had a suboptimal position of the shunt requiring a revision surgery (Table 4.12). There was reduction in the complications in the later part of the study when the opening pressure was set at 130 mm H2O and gradually reduced.

Table 4.12: Complication of shunt at 4-6 weeks

Type of complication	Initial part of study (13 patients)	Later part of study (10 patients)	Total (23 patients)	Outcome
Suboptimal proximal end of VPS	0	1 (4 %)	1	Revision of shunt
Subdural Hygroma (SDHy)	3 (13 %)	0	3	Conservatively managed
Subdural haematoma (SDH)	2 (8.7 %)	0	2	One patient needed an operation

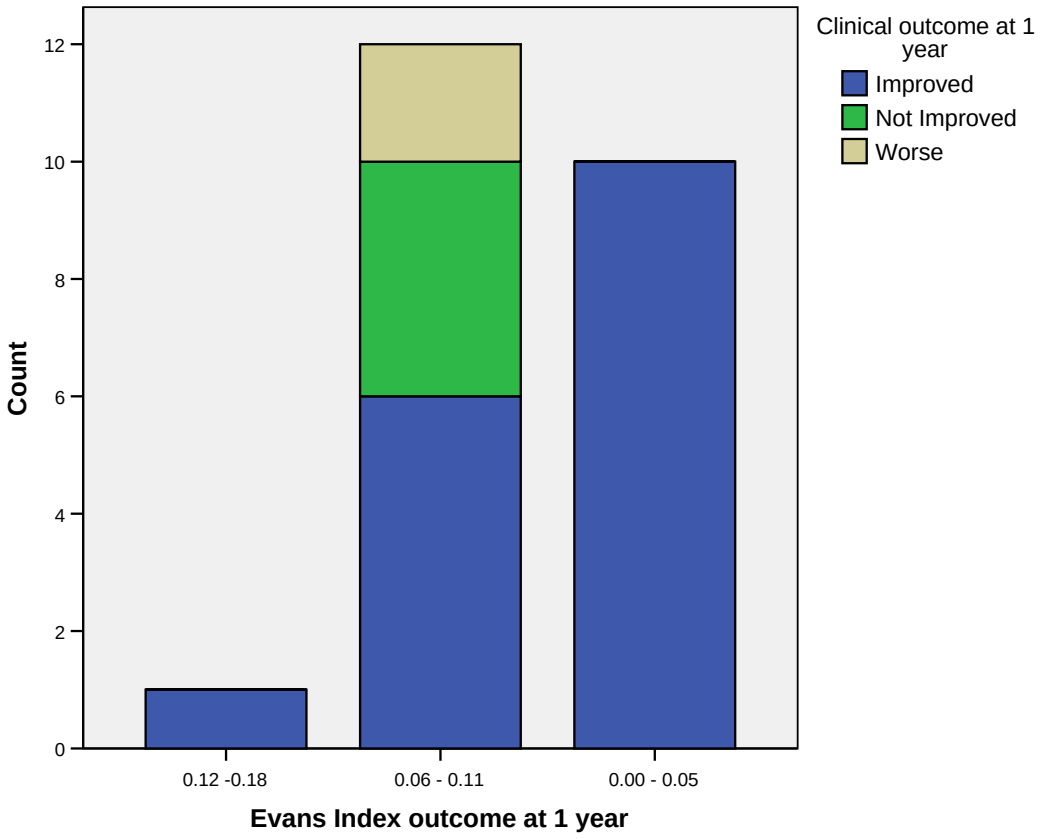
The two patients who had a repeat surgery for their complication were reviewed again after four weeks with CT scans. The shunt position was satisfactory and the subdural collection was stable with less midline shift and the weakness had improved. The patients with SDHy and SDH were managed conservatively by increasing their valve pressure to 130 mm H_2O, they remained stable without any increase in the size of their collection and one of them required a further raise in their pressure by 20 mmHg. The pressure was then gradually reduced over a period of time. Every time they had a change in their pressure setting they were reviewed 4 weeks later.

4.3.3.3 Radiology outcome at 1 year

CT studies were compared between baseline and one year in all 40 patients. In shunted patients (N=23) the mean difference between the baseline (m=0.422, SD=0.077) and one-year

Evans' index (M=0.359, SD=0.085) showed a moderate reduction in the size of the ventricle (M=0.063). A related samples t-test revealed a significant difference between the baseline and one-year Evans' index in the shunted patients ($p < 0.001$, CI=0.044-0.82). In the non-shunted patients the mean difference between the baseline (M=0.443, SD=0.120) and one-year (M=0.437, SD=0.113) Evans' index did not show a reduction in the size of the ventricles (M=0.006). A related samples t-test showed non-significant difference between the baseline and one-year Evans' index ($p=0.32$, CI=-0.21-0.33) between the shunted and the non-shunted patients (Table 4.13).

Figure 4.1: Association of Evans' index and clinical outcome at 1 year in the shunted patients.



Of the shunted patients 43.5% did not have any reduction in their ventricular size but all patients showed clinical improvement. Amongst the 52.5% patients who showed moderate reduction in their ventricular size 50% showed clinical improvement, 33% showed no improvement and 16.6% showed worsening of their symptoms. Only one patient had a significant reduction in his ventricular size with clinical improvement (Fig 4.1).

Table 4.13: Evans' index in the shunted and non-shunted patients.

	Shunted			Non-Shunted		
	Baseline EI Mean (SD)	1 year EI Mean (SD)	p-value	Baseline EI Mean (SD)	1 year EI Mean (SD)	p-value
Evans' index	0.422 (0.077)	0.359 (0.085)	0.001	0.443 (0.120)	0.437 (0.113)	0.32

At 1 year a patient showed evidence of subdural haematoma that required evacuation of the collection surgically and another patient with an SDHy was managed conservatively. The other CT features that were compared at one year were the periventricular changes and cerebral infarcts. Of the 9 patients who had periventricular changes at presentation, 5 were shunted. The periventricular changes improved in 4 and remained the same in one. The periventricular changes in the 4 non-shunted patients were unchanged at one year. Six patients had cerebral infarcts and ischemic changes at presentation. Two patients were shunted and neither improved following shunting. There were 4 more patients who showed new ischemic lesions or infarcts on the CT at one year, two of them following a shunt. Of the four patients with periventricular changes who were not shunted, one patient developed a stroke with a cerebral infarct but clinically recovered fully. The remaining three were stable clinically and radiologically.

4.3.4 Summary

A CT scan performed during the postoperative period (4-6weeks) was very useful in identifying the early complications and position of the catheter. This helped in the programming of the valve during subsequent follow-up. At one year the Evans' index showed a significant reduction (p=0.001) in the size of the ventricle in the shunted group. Periventricular changes improved in the majority of those who were shunted.

4.4 Baseline neuropsychological and gait tests

4.4.1 Aim 3

To evaluate the baseline values of the screening, neuropsychological and gait tests at presentation to determine whether there were any significant differences between the shunted and the non-shunted patients.

4.4.2 Results

4.4.2.1 NART

Premorbid IQ of patients varies within the population and it reflects on the performance of other tests. The patients in both groups were within the normal range of IQ for their age (Table 4.14). A Mann-Whitney U test failed to show any significant differences between the shunted (M=110.78, SD=7.2) and the non-shunted (M=108.76, SD=8.3) groups (U = 166.50, Z = -0.798, p = 0.212).

Table 4.14: Range of IQ between the shunted and non-shunted patients.

IQ range	Classification	Shunt (23)	No Shunt (17)
120 and over	Very superior intelligence	0	1
110-120	Superior intelligence	3	5
90-110	Normal to average	18	10
80-90	Dullness	2	1
Below 70	Borderline to severe deficiency	0	0

4.4.2.2 Beck Depression Index

Depression could affect the performance in the neuropsychological tests; severely depressed patients were referred to the psychiatrist for investigation and treatment. In total, 82.5% of the patients in the shunted (m=14.09, SD=7.6) and the non-shunted (M=14.18, SD=8.2) group were within the normal to mild range of depression (Table 4.15). One of the patients in each group had severe depression. They were both treated for their depression with anti-depressants in the first instance before any tests were performed. A Mann-Whitney test failed to show any significant differences between the shunted and non-shunted groups (U = 188.0, Z = -0.206, p = 0.85).

Table 4.15 Beck Depression Index – scores of their depression status.

	Shunted	Non-shunted	Total (percent)
Normal (5-9)	7	4	11 (27.5%)
Mild (10-18)	12	10	22 (55%)
Moderate (19-29)	3	2	5 (12.5%)
Severe (30-63)	1	1	2 (5%)
Total	23	17	40 (100%)

4.4.2.3 Mini Mental Score Examination

Thirty-one patients (77.5%) had normal to moderate level of cognitive scores and nine patients (22.5 %) had severe cognitive deficits as described in most studies (Table 4.16). The mean ages of the nine patients who had severe cognitive deficits MMSE (<13 points) were 74.8 years for the shunted and 83 years for those who were not shunted. Three of the five patients showed improvement at one year following shunting.

Table 4.16: Mini mental scores in the shunted and non-shunted patients.

Range	MMSE range	Shunt	No-shunt	Total (percentage)
Normal	25-30	6	5	11 (27.5%)
Mild impairment	21-24	4	3	7 (17.5%)
Moderate impairment	14-20	8	5	13 (32.5%)
Severe impairment	<13	5	4	9 (22.5%)
	Total	23	17	40 (100%)

4.4.2.4 CANTAB test

Unfortunately this test was abandoned after a set of 4 patients had been administered during the initial part of the study due to a variety of reasons, namely (i) difficulty to administer by the researcher due to time constrains, as each setting took more than an hour and had to be performed before and after drainage, (ii) availability of neuropsychologist with expertise in this tool, (iii) patients were not very co-operative to perform the test as some of them have never used a computer or even seen one, which again took a considerable amount of time to familiarise. Data from the 4 patients were not analysed due to the likely inaccuracy of obtaining the data. This will not be discussed further in this thesis. In future this valuable computer equipment could be used in selected patients with appropriate trained persons.

4.4.2.5 Baseline tests

The baselines values of the various tests at presentation were analysed using a Mann-Whitney U-test. This is used to compare two independent groups of sampled data. Although the

mean values for the shunted and non-shunted patients were different, a Mann-Whitney U-test failed to show any significant difference between the groups (Table 4.17).

Table 4.17: Mann-Whitney U-test results of baseline tests.

Test	Shunt	No Shunt	U	Z	P value
	Baseline Mean (SD)	Baseline Mean (SD)			
MMSE	19.57 (6.48)	19.41 (7.09)	193.50	-0.55	0.48
VF-FAS	21.61 (11.51)	28.82 (24.34)	181.00	-0.397	0.35
VF animal	9.26 (6.11)	8.18 (5.96)	178.50	-0.467	0.32
Clocks	5.09 (2.73)	5.53 (3.11)	174.50	-0.579	0.28
Gait 10 metre time	22.09 (17.66)	30.59 (21.4)	145.50	-1.375	0.08
Gait 10 metre steps	33.65 (28.26)	35.41 (28.32)	191.00	-0.124	0.45
360 deg turn time	6.74 (6.21)	8.06 (8.63)	191.00	-0.125	0.45
360 deg turn steps	8.61 (8.36)	7.41 (6.76)	181.00	-0.404	0.34

Table 4.18: Pearson Correlation coefficients for the neuropsychological and gait tests of all participants

Variable	MMSE	VF	VFanimal	Clock drawing	Time to walk 10 metre	No of steps to walk 10 metre	Time taken to turn 360 degree	No of steps to turn 360 degree
MMSE	1	.583**	.739**	.608**	.140	.270	-.093	.009
	-	.000	.000	.000	.388	.092	.569	.956
VF	-	1	.540**	.400*	.223	.225	-.005	.228
	-	-	.000	.011	.167	.163	.975	.157
VFanimal	-	-	1	.574**	.293	.246	-.173	-.137
	-	-	-	.000	.066	.126	.287	.399
Clock drawing	-	-	-	1	.212	.207	.027	.222
	-	-	-	-	.188	.200	.870	.169
Time to walk 10 metre	-	-	-	-	1	.780**	.507**	.377*
	-	-	-	-	-	.000	.001	.017
No of steps to walk 10 metre	-	-	-	-	-	1	.513**	.444**
	-	-	-	-	-	-	.001	.004
Time taken to turn 360 degree	-	-	-	-	-	-	1	.598**
	-	-	-	-	-	-	-	.000
No of steps to turn 360 degree	-	-	-	-	-	-	-	1
	-	-	-	-	-	-	-	-

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 4.18 tabulates the Pearson correlation for the neuropsychological and gait tests. This was to measure the strength or degree of a supposed linear association between two variables. It can be concluded from this data that the correlation coefficients were significant between all the neuropsychological tests with 2-tailed p-values less than 0.01 and between the gaits tests with 2 tailed p-values less than 0.01. However there was no correlation between the neuropsychological and gait tests.

4.4.3 Summary

The screening tests and baseline tests used in the study did not discriminate between the shunted and non-shunted groups and there was no correlation between the neuropsychological and gait tests.

4.5 CSF hydrodynamic studies

4.5.1 Introduction

During an infusion study the opening pressure of CSF and plateau pressure were measured to calculate the Rcsf. An external lumbar drain was inserted for 2 days following the infusion study. Neuropsychological and gait tests were repeated after drainage. An Rcsf of >12mmHg/ml/min was used as a positive criteria for shunting. In this section the results of the lumbar infusion studies are analysed.

4.5.2 Aim 4

To evaluate the usefulness of Rcsf value as a criteria for shunting and to analyse the outcome of the shunted patients with an Rcsf of 12mmHg/ml/min or more.

4.5.3 Results

4.5.3.1 Opening and Plateau pressure

The average opening and plateau pressures measured in shunted and non-shunted patients are summarised in Table 4.19. There was no difference in the opening pressure between the two groups of patients. The average opening pressures for iNPH and sNPH patients were 9.38mmHg (range 3-17mmHg) and 10.33 mmHg (7-14 mmHg) respectively.

Table 4.19: Opening and plateau pressures in the shunted and non-shunted patients.

	Shunt (mm Hg)		No Shunt (mm Hg)	
	Mean (SD)	Range	Mean (SD)	Range
Opening Pressure	9.22 (3.4)	3-17	9.94 (3.9)	3-17
Plateau Pressure	31.43 (9.8)	14-55	27.29 (11.5)	6-50

4.5.3.2 Rcsf

Following the infusion studies, the Rcsf was calculated. An Rcsf of 12mmHg/ml/min was used as positive criteria for shunting. The average Rcsf values in the shunted and non-shunted group are shown in Table 4.20; Table 4.21 shows the number of patients with different ranges of Rcsf in mmHg/ml/min (<11.9, 12-17.9, >18). The majority of patients in the shunted group had an Rcsf of more than 18mmHg/ml/min (43.5%). Seven patients with Rcsf of less than 12 mmHg/mil/min were also shunted and 8 patients of those with an Rcsf of more than 12 mmHg/mil/min were not shunted. Considering an Rcsf of 12mmHg/ml/min as a cut off, 60% of the patients showed improvement in the neuropsychological and gait tests following an ELD (Figure 4.2). This clearly shows that Rcsf should not be used on its own as a criterion for shunting in this study.

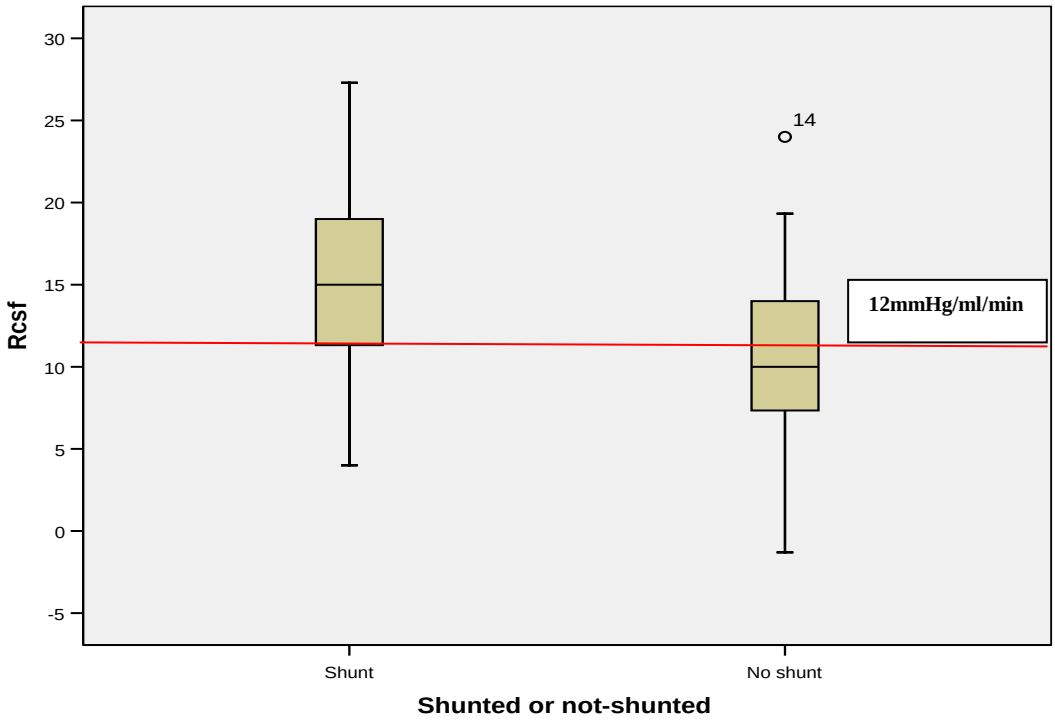
Table 4.20: Rcsf values in the shunted and non-shunted patients

Treatment (n=40)	Rcsf in mmHg/ml/min-Mean (SD)	Range mmHg/ml/min
Shunted (n=23)	14.9 (5.43)	4 - 27.3
Non-Shunted (n=17)	9.7 (6.4)	-1.30 – 24

Table 4.21: Range of Rcsf in shunted and non-shunted patients.

Rcsf : mmHg/ml/min	Total	Shunted		Non-Shunted	
< 11.9	16	7	30.5%	9	53%
12-17.9	10	6	26%	4	23.5%
>18	14	10	43.5%	4	23.5%
Total	40	23	100%	17	100%

Figure 4.2: Box plot of Rcsf values in shunted and non-shunted patients.



As predicted the mean Rcsf of the shunted (n=23, M = 14.9, SD = 5.43) patients was higher than the non-shunted (n = 17, M = 9.7, SD = 6.4). The difference is significant beyond the 0.05 level: t (38) = 2.30; p = 0.014. The 95% confidence interval on the difference between means is (0.529, 8.268). Table 4.22 shows that 63% of patients showed improvement at 1 year when an Rcsf of 12 mmHg/ml/min or more was used. Four percent did not improve and 13% had a worse outcome. Forty two percent of patients showed improvement with an Rcsf of 18 mmHg/ml/min. An Rcsf of 18 mm Hg/ml/min was used as an example to calculate this in the shunted group of patients (Table 4.23). The positive and negative predictive values of Rcsf were investigated by means of efficacy analysis.

Table 4.22: Rcsf and outcome of the shunted patients.

Shunted patients		Outcome at 1 year			Total
		Improved	Not-improved	Worse	
Rcsf	>18	8(42%)	0	2(9%)	10
	12-18	4(21%)	1(4%)	1(4%)	6
	<12	7(37%)	0	0	7
Total		19 (83%)	1 (4%)	3 (13%)	23

Table 4.23: Efficacy analysis at Rcsf of 18 mmHg/ml/min

Rcsf : >18mmHg/ml/min	Shunt responsive	Shunt Non responsive	Total
Test Positive	8 (a)	2 (b)	10
Test Negative	9 (c)	4 (d)	13
Total	17	6	23

1. Sensitivity = a/(a+c) = 8/17 = 47%
2. Specificity = d/(b+d) = 4/6 = 66%
3. Likelihood ratio of positive result = Sensitivity/(1-specificity) =0 .47/1-0.66= 1.38
4. Positive predictive value = a/(a+b) = 8/10 = 80%
5. Negative predictive value = d/(c+d) = 4/13 = 31%
6. Prevalence of shunt responsive (SR) hydrocephalus = (arc)/(a+b+c+d) = 17/ 23 = 74%
7. Pre-test odds of having SR hydrocephalus = Prevalence / (1-prevalence) = 0.74/(1-0.74) = 2.8
8. Post-test odds of having SR hydrocephalus = pre-test odds x likelihood ratio = 2.8 x 1.38 = 3.86
9. Post test probability of having SR hydrocephalus = post test odds/(post test odds+1) = 3.86 / 4.86 = 79%

The specificity was 83% and sensitivity was 17% if the Rcsf was raised to 20mmHg/ml/min with a positive predictive value of 75% and the likelihood ratio was 1.0. The specificity and positive predictive ratio was 100% if the Rcsf was raised to 24mmHg/ml/min. Because of the considerable number of patients who improved despite a negative test, the

negative predictive values were low. In Table 4.24, sensitivity decreased and specificity increased with rising Rcsf values. The highest likelihood ratio (sensitivity/100 - specificity) was by far was found at an Rcsf cutoff of 18 mm Hg/ml/minute with a positive predictive value of 80%. If there was a big change in the pre-test to post-test odds then it would be more clinically useful but this was not noticed. The post-test probability of having a shunt response was 68%.

Table 4.24: Diagnostic testing of Rcsf values.

Rcsf mm > = Hg/ml/min	Sensitivity (%)	Specificity (%)	Likelihood Ratio	Positive predictive value (%)	Negative predictive value (%)
12	64	16	0.76	68	14
18	47	66	1.38	80	31
20	17	83	1.0	75	26
24	5	100	∞	100	27

Although Rcsf was only part of the criteria for shunting, at 1 year a paired samples t-test showed a significant difference between the shunted and the non-shunted groups in all the neuropsychological tests and some of the gait tests with p values < 0.05. The results are summarised in Table 4.25.

Table 4.25: Outcome at 1 year with an Rcsf above and below 12mmHg/ml/min in the shunted and non shunted patients.

	Rcsf >/= 12 mmHg/ml/min			Rcsf < 12 mmHg/ml/min		
Drainage	Baseline Mean (SD)	1 year Mean (SD)	p-value	Baseline Mean (SD)	1 year Mean (SD)	p-value
MMSE	17.21 (6.26)	19.38 (5.97)	0.004*	22.94(5.85)	23.81(5.67)	0.138
VF FAS	19 (11.43)	22.21 (12.79)	0.006*	33.19(23.05)	29.81(19.3)	0.056
VF animal	7.13 (4.0)	9.08 (5.32)	0.005*	10.50(7.04)	11.31(6.18)	0.151
Clocks	4.67 (3.05)	5.29 (3.13)	0.05*	6.19(2.4)	6.31(2.15)	0.379
10 metre time	23.50(20.6)	23.33(22.43)	0.487	29.0(17.96)	28.50(12.96)	0.45
10 metre Steps	29.71(25.97)	23.67(18.71)	0.045*	41.44(30.12)	31.75(21.45)	0.655
360° turn time	8.21(7.59)	9.25(9.48)	0.256	5.94(6.76)	6.31(5.21)	0.434
360° turn steps	8.13(6.89)	5.33(4.59)	0.002*	8.06(8.91)	9.56(6.83)	0.108

* $p < 0.05$

4.5.4 Summary

At an Rcsf value of 12 mmHg/ml/minute positive predictive values for improvement were approximately 68% with a specificity of 16% and sensitivity 64%. At one year there was a significant difference between the shunted and the non-shunted patients in majority of the supplementary tests used with 63% patients showing improvement.

4.6. Effects of ELD on patient selection

4.6.1. Introduction

All patients included in the study had a lumbar puncture and CSF studies as mentioned in the previous chapter. Following this, an ELD was placed for 2 days. Neuropsychological tests, gait tests, subjective improvement in the urinary symptoms and Rcsf results were used to classify patients into 3 categories: probable, possible and unlikely. Table 3.3 shows how these categories were derived. The patients in the probable category were shunted, those in the possible category were given the option of a shunt and the patients in the unlikely category were not shunted. In this section we will discuss these results in detail.

4.6.2 Aim 5

To determine whether the effects of external lumbar drain (ELD) on supplemental neuropsychological and gait tests along with urinary symptoms and to determine if there is any correlation between the tests which are used to select patients for shunting at 1 year.

4.6.3 Outcome of ELD selection

Twelve out of 40 patients with NPH improved (30%) following ELD. Nineteen patients (48%) showed some improvement. These groups of patients have also been referred to as borderline improvement groups in some series. Nine patients (22%) did not improve in the majority of the tests and none of them had a shunt (Table 4.26). These patients were classed as probable, possible and unlikely. Of the 12 (30%) patients in the probable group 11 (92%) were shunted and one patient refused a shunt as he did not want to take the risks of the operation. Twelve (63%) patients were shunted in the possible group and seven (37%) refused a shunt operation. All of the nine patients who were unlikely to improve were not shunted.

Table 4.26: Outcome of ELD.

ELD outcome	Total	Shunt		No shunt	
Probable	12 (30%)	11	92%	1*	8%
Possible	19 (48%)	12	63%	7	37%
Unlikely	9 (22%)	0	0%	9	100%
Total	40 (100%)	23	-	17	-

*Patient refused a shunt operation.

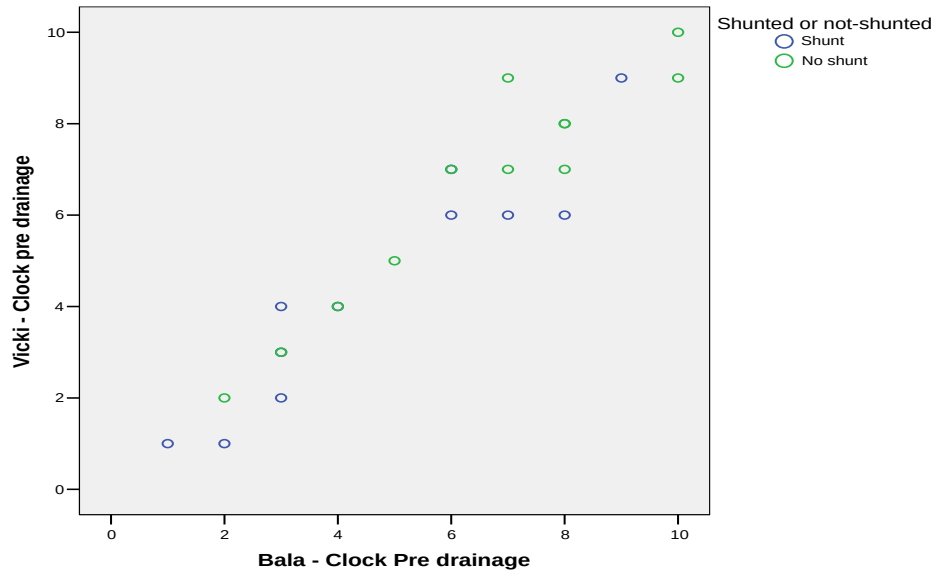
4.6.4 Effect of ELD on neuropsychological and gait tests

From the short-term drainage the mean difference values for the various tests were significant in the shunted patients for most of the neuropsychological and gait tests. A related-samples t-test showed significance beyond the 0.05 level for all of the neuropsychological tests and most of the gait tests except the 10 metre walking time and 360 degree turning time. These results are shown in Table 4.27. The non-shunted patients did not show any significant difference in any of the tests. This confirms that the patients were selected based on the significant improvement in the various tests and the high predictive value of ELD in the probable and possible groups.

Table 4.27: Outcome of all the tests in the shunted and non-shunted group

	Shunted			Non-Shunted		
Drainage	Pre drainage Mean (SD)	Post drainage Mean (SD)	p-value	Pre drainage Mean (SD)	Post drainage Mean (SD)	p-value
MMSE	19.57 (6.48)	21.83 (6.44)	0.0001	19.41(7.09)	19.59(8.25)	0.442
VF FAS	21.61(11.51)	25.87(13.31)	0.0025	28.82 (24.34)	23.71 (22.0)	0.019
VF animal	8.09 (5.42)	9.26 (6.11)	0.054	9.0 (5.96)	8.18(4.94)	0.188
Clocks	5.09 (2.75)	5.91 (2.73)	0.01	5.53 (3.11)	5.65 (3.30)	0.415
10 metre time	22.09(17.66)	19.70(15.94)	0.191	30.59(21.4)	34.59(48.64)	0.34
10 metre Steps	33.65(28.26)	26.35(20.34)	0.049	35.41(28.32)	36.65(35.31)	0.394
360° turn time	6.74 (6.22)	6.48 (6.89)	0.423	8.06(8.63)	7.35(10.94)	0.36
360° turn steps	8.61 (8.36)	6.04 (5.73)	0.026	7.41(6.76)	6.41(6.33)	0.159

The pre and post drainage clock drawing tests were compared for inter-rater reliability. A second observer scored the clock tests and Pearson correlation coefficient between observer scores was positive at 0.95. The linear scatter plot in Figure 4.3 shows a deviation to the right with narrow elliptical clouding of the points and was significant (p=0.001)



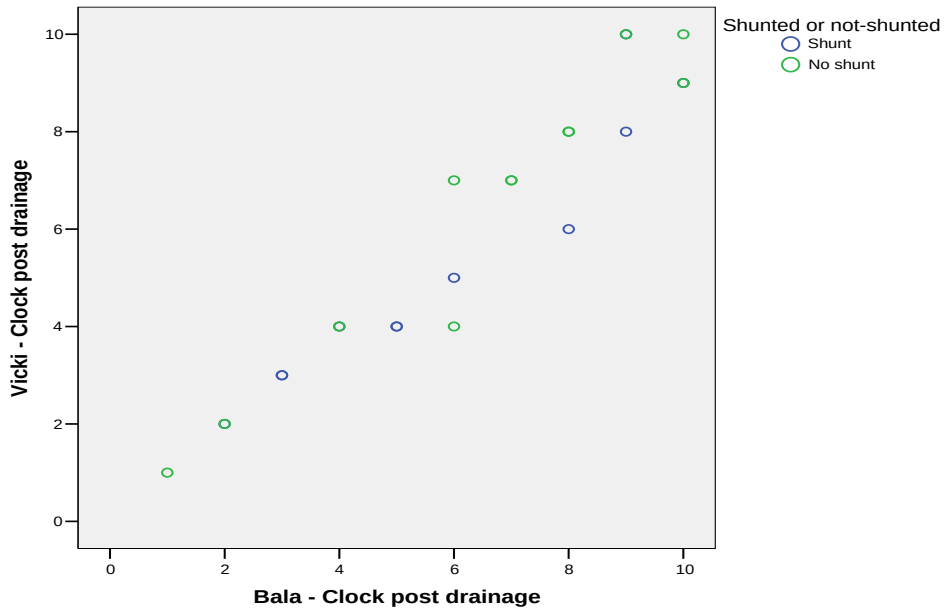


Figure 4.3: Inter-rater reliability in clock drawing tests pre and post drainage.

4.6.5 Outcome of shunted and non-shunted ELD positive patients at 1 year

4.6.5.1 Shunted patients

Table 4.28: Outcome at 1 year for the shunted patients with probable and possible improvement

	Total shunted	Improved	Not improved	Worse
Probable	11 (48%)	8	2	1
Possible	12 (52%)	9	2	1
Unlikely	0	0	0	0
Total	23 (100%)	17 (74%)	4(17%)	2(9%)

Eleven patients (48%) were classified in the probable improvement category of which 8 (35%) had improvement at 1 year. Of the 12 (52%) in the possible class 9 (39%) improved at 1 year. The remaining 4 (17%) did not improve but were no worse than their presentation and 2 (9%) worsened after shunting (4.28).

4.6.5.2 Non-shunted patients

It is interesting to review the non-shunted patients in a similar way. One patient as mentioned earlier refused a shunt showing improvement following ELD. This patient did not get worse but remained symptomatic. Of the 7 patients (42%) in the possible group 5 of them worsened (71%) and only 1 (14%) showed some improvement despite not being shunted. Sixty seven percent of those in the unlikely class worsened and 3 (33%) remained symptomatic (4.29).

Table 4.29: Outcome at 1 year for the non-shunted patients

	Total	Improved	Not improved	Worse
Probable	1 (5%)	0	1	0
Possible	7 (42%)	1	1	5
Unlikely	9 (53%)	0	3	6
Total	17 (100%)	1(5%)	5(29%)	11(66%)

It cannot be proved if the non-shunted patients who also had a reliable clinical and radiological presentation would have benefited from a shunt but clearly they showed no improvement from conservative management except one patient (5%). NPH is not a progressive disease and not self-limiting. The likelihood of these patients showing any improvement with a shunt despite having a negative test is unlikely.

4.6.5.3 ELD re-testing in non-shunted patients

There is no evidence in the literature if retesting is useful or essential before the patients can be declined a shunt treatment. In this study 14 non-shunted patients were worse at 6 months. Only 2 patients were retested and 12 patients declined for various reasons. This could partly be due to the reason that they have accepted the fact that no treatment will change the outcome and also from the experience of having the lumbar puncture and other tests in hospital they preferred not to have the same repeated. The 2 patients who were retested showed no improvement in their symptoms and they were followed up.

4.6.5.4 Summary

ELD was a good predictor of which NPH patients may have benefited from a shunt. Following ELD testing, categorising patients into probable, possible and unlikely seemed to be the best method to study the groups and to compare the within group analysis.

4.7 Outcome at 6 months and 1 year

4.7.1 Introduction

In this study the patients have been followed up at 6 months and 1 year. A further follow up of the outcome of all patients is proposed at 2 and 5 year intervals.

4.7.2 Aim 6

To examine the effects of shunting to determine whether the symptoms of NPH improve following surgery. The control group (those not receiving a shunt) were reassessed after the same time period to determine which factors alter over time.

4.7.3 Results

All patients were followed up for a period of 1 year. Those who were not shunted were used as a control group (Table 4.30). This allowed the determination of those factors that altered over time. Data were analysed using a 2 (treatment: shunt, no shunt) x 3 (assessment time 1, time 2 & time 3) mixed analysis of variance (ANOVA) for between and within subjects factors for each of the measures used. Time 1-3 were outcome points post-drain, at 6 months and at 1 year. This test allows the examination of the effects of shunting and determines whether the symptoms of NPH improve following surgery.

Table 4.30: Clinical outcome at 6 month and 1 year

	Outcome at 6 months			Outcome at 1 year		
	Improved (%)	Not Improved (%)	Worse (%)	Improved (%)	Non Improved (%)	Worse (%)
Shunted	10 (43)	11 (48)	2 (9)	17 (74)	4 (17)	2 (9)
Non-shunted	1 (6)	2 (12)	14 (82)	1 (6)	5 (29)	11 (65)

The mean scores for the patients selected for shunt and those not selected differed significantly in all the neuropsychological tests: MMSE ($F(1, 38) = 4.53$, $p=0.04$); verbal fluency-FAS ($F(1, 38) = 26.27$, $p<0.0001$); verbal fluency – animals ($F(1, 38) = 14.63$, $p<0.0001$); clock drawing ($F(1, 38) = 4.53$, $p=0.04$). Similarly there was significant differences between these two groups of patients on the 360 degree step count ($F(1,38) = 4.42$, $p=0.04$); but the other gait tests did not show any significant differences between the shunted and the non-shunted patients, time for 10 metre walk ($F(1,38) = 2.69$, $p=0.109$); steps in 10 metre walk ($F(1,38) = 0.793$, $p=0.379$) and time taken to turn 360degrees ($F(1,38)=0.182$, $p=0.672$) (Table 4.37).

		Post Drainage			6 months			12 months		
		Shunted Mean(SD)	No-Shunt Mean(SD)	P (CI)	Shunted Mean(SD)	No-Shunt Mean(SD)	P (CI)	Shunted Mean(SD)	No-Shunt Mean(SD)	P (CI)
Memory Tests	MMSE	2.26 (2.58)	0.18 (4.90)	0.089 (-0.37,4.51)	2.70 (3.28)	0.47 (3.24)	0.04* (0.11,4.34)	2.43 (3.15)	0.59 (3.69)	0.096 (-0.35,4.04)
	VF (FAS)	4.26 (6.62)	-5.12 (9.31)	0.001* (4.29,14.47)	5.43 (5.75)	-4.47 (8.63)	0.0001* (5.30,14.51)	4.61 (5.20)	-4.88 (6.42)	0.0001* (5.77,13.21)
	VF (animal)	1.17 (3.35)	-0.82 (3.73)	0.084 (-0.28,14.5)	2.74 (2.88)	-0.24 (2.84)	0.002* (1.12,4.83)	3.13 (2.46)	-0.71 (2.87)	0.0001* (2.13,5.54)
	Clocks	0.83 (1.59)	0.12 (2.21)	0.244 (-0.5,1.92)	0.96 (1.69)	0.35 (1.54)	0.254 (-0.45,1.66)	1.04 (1.67)	-0.41 (1.42)	0.006* (0.44,2.47)
Gait tests	10 metre time	6.39 (11.31)	-4.0 (39.26)	0.234 (-7.02,27.8)	11.48 (17.31)	4.71 (20.61)	0.266 (-5.38,18.93)	12.09 (18.01)	4.71 (19.46)	0.223 (-4.6,19.45)
	10 metre steps	7.30 (20.24)	-1.24 (18.59)	0.180 (-4.13,21.2)	6.57 (25.13)	4.59 (23.95)	0.803 (-13.98,17.93)	9.48 (19.11)	4.82 (21.08)	0.470 (-8.3,17.58)
	360° turn time	0.26 (6.33)	0.7 (7.97)	0.845 (-5.02,4.13)	-0.61 (9.14)	-4.47 (9.99)	0.212 (-2.3,10.12)	-1.09 (7.75)	-0.35 (8.65)	0.780 (-6.0,4.54)
	360° turn steps	2.57 (6.0)	1.0 (4.0)	0.357 (-1.84,4.97)	1.43 (7.48)	-3.24 (5.29)	0.034 (0.37,8.97)	2.52 (5.32)	-0.88 (3.0)	0.023* (0.5,6.3)

*P <0.05, CI 95%

Table 4.31: Outcome of the supplemental tests over time in all patients.

Table 4.32: Clinical improvement at 6 months and 1 year

		Outcome at 6 months			Outcome at 1 year		
		Improved	Not Improved	Worse	Improved	Not Improved	Worse
Shunted	Memory	9 (39%)	9 (39%)	5(22%)	18 (78%)	4(18%)	1(4%)
	Gait	12(52%)	8(35%)	3(13%)	19 (83%)	3(13%)	1(4%)
	Urinary	9 (39%)	14(61%)	0(0%)	6 (26%)	16(70%)	1(4%)
Not Shunted	Memory	2(12%)	4(23%)	11(65%)	4(24%)	7(41%)	6(35%)
	Gait	2(12%)	3(18%)	12(70%)	6(35%)	7(41%)	4(24%)
	Urinary	0(0%)	13(77%)	4(23%)	0(0%)	14(82%)	3(18%)

Maximum shunt setting alteration in the shunted patients was performed during their review at 6 months and after. This explains the clinical improvement seen at 1 year compared to 6 months. Maximum improvement was seen in their gait (83%) and memory (78%) symptoms and only 26% improved in urinary symptoms (Table 4.32).

The non-shunted patients showed no improvement at 1 year although interestingly 6 patients showed some improvement in their gait and memory symptoms. We are unable to explain this improvement despite the fact that these patients had no intervention. The numbers are too small to draw any conclusions.

4.7.4 Summary

At one year there were differences between the shunted and the non-shunted patients in all the neuropsychological tests, with statistically significant differences noted in the verbal

fluency test ($p<0.0001$) and clock drawing test. The gait tests did not show any significant differences except the 360 degrees turn ($p=0.04$). The non-shunted patients showed no improvement at 1 year. At 1 year 78% improved in their memory and 83% improved in their gait tests compared to 39% and 52% at 6 months. The improvement seen between 6 months and 1 year can be explained by the change in the valve pressure settings when no clinical improvement was seen. Urinary symptoms slightly worsened at 1 year from 39% to 26%. Overall there was a very slight improvement in the non-shunted patients.

4.8 Shunt responsive patients

4.8.1 Introduction

Because CSF diversion carries a significant risk of mortality and morbidity it is important to analyse the patients who were shunted to see those who improved, to develop a set of standard tests. The methods chosen in this study to analyse this is the mixed analysis of variance and regression analysis within the shunted group of patients.

4.8.2 Aim 7

To compare the selection criteria including ELD, Rcsf values and outcome of the shunted patients who have responded well to surgery, with those who show little or no improvement. Within group analysis may assist in developing criteria, in the future, to select patients who are most likely to benefit from surgery.

4.8.3 Results

Data were analysed using a 2 (surgery: improved, not improved) x 3 (assessment time 1, time 2 & time 3) mixed analysis of variance (ANOVA) for between and within subjects factors for each of the measures used. Time 1-3 were outcome points post-drain, at 6 months and at 1

year. The mean scores for the patients who showed improvement with those who did not improve differed significantly in all the neuropsychological tests except the MMSE, ($F(1, 38) = 2.5$, $p=0.122$); verbal fluency-FAS ($F(1, 38) = 14.84$, $p<0.0001$); verbal fluency – animals ($F(1, 38) = 13.7$, $p<0.001$) clock drawing test ($F(1, 38) = 5.35$, $p=0.026$). Similarly there were significant differences between these two groups of patients on the 10 metre walking time ($F(1,38) = 9.04$, $p=0.005$); but the other gait tests did not show any significant differences between the shunted and the non-shunted patients, steps in 10 metre walk gait ($F(1,38) = 0.19$, $p=0.665$); time taken to turn 360degrees ($F(1,38)=0.71$, $p=0.406$); number of steps to turn 360degrees ($F(1,38)=0.410$, $p=0.526$) (Table 4.39).

		Post Drainage			6 months			12 months		
		Improved Mean(SD)	Not-Improved Mean(SD)	P (CI)	Improved Mean(SD)	Not-Improved Mean(SD)	P (CI)	Improved Mean(SD)	Not-Improved Mean(SD)	P (CI)
Neuropsy. Tests	MMSE	2.61 (2.77)	0.36 (4.33)	0.064 (-0.14,4.64)	2.56 (3.55)	1.09 (3.22)	0.18 (-0.71,3.64)	2.17 (3.19)	1.23 (3.7)	0.40 (-1.3,3.18)
	VF (FAS)	4.56 (6.21)	-3.23 (9.65)	0.0005* (2.45,13.12)	5.89 (4.83)	-2.59 (9.18)	0.001* (3.62,13.34)	4.67 (5.13)	-2.77 (7.37)	0.001* (3.28,11.6)
	VF (animal)	1.72 (3.39)	-0.82 (3.45)	0.025* 0.34,4.74)	2.94 (2.92)	0.27 (2.95)	0.007* (0.78,4.56)	3.33 (2.17)	0.00 (3.22)	0.001* (1.53,5.14)
	Clocks	0.78 (1.40)	0.32 (2.21)	0.449 (-0.76,1.68)	1.28 (1.67)	0.23 (1.48)	0.042* (0.041,2.06)	1.22 (1.67)	-0.23 (1.48)	0.006* (0.44,2.47)
Gait tests	10 metre time	6.72 (12.27)	-1.91 (34.66)	0.322 (-8.76,26.0)	17.33 (20.66)	1.45 (13.95)	0.006* (4.76,26.99)	18.33 (22.96)	1.27 (9.48)	0.003* (6.19,27.93)
	10 metre steps	8.28 (22.82)	-0.09 (16.48)	0.187 (-4.2,20.96)	4.33 (30.22)	6.86 (18.93)	0.748 (-18.38,13.3)	8.39 (23.23)	6.77 (17.12)	0.801 (-11.3,14.5)
	360° turn time	-0.33 (6.86)	1.09 (7.17)	0.528 (-5.95,3.1)	-3.0 (13.3)	-1.64 (5.67)	0.660 (-7.59,4.87)	-2.11 (9.06)	0.32 (7.13)	0.349 (-7.61,2.75)
	360° turn steps	2.33 (6.34)	1.55 (4.26)	0.642 (-2.62,4.2)	-0.39 (8.97)	-0.68 (4.99)	0.897 (-4.25,4.83)	2.17 (5.47)	0.18 (3.97)	0.192 (-1.04,5.01)

*P < 0.05

Table 4.33: Outcome of the supplemental tests over time in the shunted patients.

4.8.4 Summary

These results show that within the shunted group all but the MMSE neuropsychological tests and the 10 metreetre walking test were good predictors of surgical success with shunt. The MMSE as discussed in chapter 3.4.4 is a good screening test to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes over time or response to treatment. These tests can be used in assessing future patients.

4.9 Prediction of surgical success in shunted patients

4.9.1 Aim 8

To investigate if any of the neuropsychological or gait tests at baseline were able to predict surgical success or failure in the shunt improved patients at 1 year.

4.9.2 Results

A multiple regression analysis was conducted with outcome from presentation to 1 year as the dependent variable and MMSE, VF-FAS, VF-animals and clock drawing tests as the predictor variables. The model accounted for 15.3% of the variance. Only verbal fluency-FAS at baseline predicted improvement (β=0.403, p=0.047). Table 4.34 shows the standardized coefficients (β) and the p values of the other predictors.

Table 4.34: Regression analysis of the memory tests

Predictors	Standardized coefficients (β)	P value (p)
MMSE at admission	-0.151	0.559
VF-FAS at admission	0.403	0.047
VF-animal at admission	-0.197	0.421
Clock drawing at admission	0.252	0.219

Similarly a regression analysis for the various gait tests was performed with outcome from presentation to 1 year as the dependent variable and 10 metre time, 10 metre steps, 360 degree turn time and number of steps to turn 360 degree tests as the predictor variables. The model accounted for 7.7%. There was no gait test that predicted improvement. The standardized coefficients (β) and the p values of the other predictor are shown in table 4.35.

Table 4.41: Regression analysis of the gait tests

Predictors (at admission)	Standardized coefficients (β)	P value (p)
Time taken for 10 m	0.370	0.171
No of steps for 10 m	-0.365	0.186
Time taken to turn 360 deg	-0.003	0.990
No of steps to turn 360 deg	-0.112	0.593

4.9.3 Summary

A multiple regression analysis of memory and gait tests at 1 year showed the VF-FAS test to be the only variable that predicted a better outcome. Similarly a multiple regression analysis conducted for the gait tests failed to show any variable that would predict improvement.

4.10 Complication of ELD and shunt

4.10.1 Introduction

External lumbar drain and the shunt insertion are both invasive procedures and can have complications related to it. This significantly determines the outcome of the condition in this group of patients who may present with other medical co-morbidities. After the shunting procedure pressure change in the programmable valve can be associated with formation of subdural collection which may be serious enough to warrant further surgery to remove it. In this section complications from these procedures are reviewed. Anticoagulants cause serious risk of bleeding both at the time of lumbar puncture and surgery. There is a small increase in risk of bleeding when they develop subdural haematomas or hygromas.

4.10.2 Aim 9

To identify the complications occurring from external lumbar drain, shunt and use of anticoagulants.

4.10.3 Results of complications of ELD

Two patients (5%) developed symptoms of meningits, one had grown staphylococcus aureus and both were treated with antibiotics. Three patients (7.5%) had their lumbar drain idisconnected and had their ELD re-inserted. Two patients (5%) developed headaches and were

treated for their symptoms (Table 4.36). There were no bleeding complications related to the use of external lumbar drain.

Table 4.36 Complication of external lumbar drain.

Complication	Number of patients	Treatment
Meningitis	2 (5%)	Antibiotics
Disconnection of drain	3 (7.5%)	Re-insertion of drain
Headaches	2 (5%)	Analgesia only

4.10.4 Results of complication from the shunt

Of the 23 patients who were shunted only one patient had a shunt revision 2 days following suboptimal position of the brain catheter. No shunt related infections were seen (Table 4.37). The major complication following shunt in this group of patients was subdural collection.

Table 4.37: Shunt related complications.

Complication	Number (percentage)	Action
Suboptimal position of ventricular catheter	1/23 (4.3%)	Revision surgery of shunt
Subdural hygroma	4/23 (17%)	Shunt pressure raised by 30 mm H2O. Conservative management only.
Subdural haematoma	3/23 (13%)	2 patients - Burr-hole evacuation of subdural haematoma. 1 patient – Shunt pressure raised

4.10.5 Anticoagulants use in NPH patients

The bleeding complications can be prevented by stopping anticoagulants before a lumbar puncture and shunt. The risk of developing serious subdural haematomas is significantly increased in those who are on anticoagulants. Shunt programming in these groups of patients should be taken with extreme care. Anticoagulants were stopped at least 10 days prior to lumbar puncture in the case of Aspirin and Clopidogrel and 5 days for those on Warfarin till the International Normalised Ratio (INR) was below 1.2. A small risk of bleeding was explained to the patients. Table 4.38 and 4.39 shows the number of patients on anticoagulants. None of the patients were refused investigation or surgery based on their anticoagulation status. One of the shunted patients on warfarin developed a subdural hematoma that did not require surgery and was managed with raising the shunt pressure. The INR control in this patient was good. There were no other complications related to the use of anticoagulants in this study. There was no evidence of intracerebral haematoma or shunt related infection.

Table 4.38: Anticoagulant use in all patients

	Shunted n = 23		Non-Shunted n = 17		Total n = 40	
Anticoagulant	5	12.5%	3	7.5%	8	20%

Table 4.39: Type of anticoagulant used

Anticoagulant	Shunted n = 23	Non-Shunted n = 17
Aspirin	3	2
Warfarin	2	0
Clopidogrel	0	1

4.10.6 Summary

Of the 40 patients who had an ELD, 7 patients developed complication of meningitis, disconnection and low pressure post drainage headaches. They were all managed conservatively and recovered fully. There was no mortality with shunts and 17% patients developed SDHy and 13% developed SDH. Surgical evacuation was needed in only 2 (8%) of patients. Use of anticoagulants did not increase morbidity when they were carefully managed.

4.11 Value of programmable shunt

4.11.1 Aim 10

To identify the value of using the programmable shunts.

4.11.2 Results of shunt programming

During the intial part of the study, the pressure set at insertion of the shunt was based on the opening pressure at lumbar puncture during assessment. This accounted for 13 patients and the reminder of the 10 patients had their pressures set at 130 mm H_2O and gradually reduced following surgery. Five patients (38%) developed subdural haematoma and hygroma, 3 of these patients developed a subdural hygroma on CT which was managed conservatively by raising their programmable pressure by 20 mmH_2O. Of the 2 other patients who developed a subdural haematoma, one of them presented with a mild right sided weakness and a left sided subdural haematoma with some mass effect and midline shift requiring surgery for evacuation of the haematoma. The other patient was managed conservatively with increasing the shunt pressure to 130 mm H_2O. Table 4.40 shows the reasons for the pressure changes performed in the shunted patients.

Table 4.40: Reasons for adjusting the valve pressure

Reasons for adjustment	Initial part of study n = 13	Later part of study n =10	All patients n = 23
Over drainage	2	0	2
Under drainage	10	14	24
Over drainage causing SDH or SDHy	5	2	7
Under drainage after SHD or SDHy	3	1	4
Altered by MRI	2	0	2
Total	22	17	39

In the later part of the study only 2 patients developed a subdural haematoma, 1 (10%) patient showed evidence of subdural haematoma with a minimal midline shift and another developed a subdural hygroma. Both were managed conservatively in the first instance, later, the patient with the subdural haematoma showed clinical deterioration and was operated with good results. One patient had a suboptimal position of the shunt and had to undergo a revision operation for repositioning the ventricular catheter.

4.11.3 Summary

Programmable shunts are useful in managing over and under drainage after insertion of a shunt. There was a 28% reduction in the SDH formation following the change in the way the shunts were programmed.

Chapter 5 Discussion

5.1 Introduction

In this section each of the aims 1 to 10 of the study are discussed. The aims are repeated followed by discussion and a brief summary.

5.2. Demographics and Clinical presentation

5.2.1 Introduction

The demographic and clinical characteristics of patients selected for shunting and those who were not plays a major role in determining the outcome as discussed in section 1.3. Clinical presentation influences the selection for shunting considering the risk:benefit ratio of shunt surgery. Whether criteria can be developed to distinguish patients suffering from NPH from those who may be suffering from other disorders with similar presentation, and the relevance of clinical presentation and outcome between the shunted and non-shunted groups of patients is also discussed.

5.2.2 Aim 1

To compare the demographic and clinical characteristics of patients who are selected for shunting with those who are not. This may provide clearer criteria to distinguish patients suffering from NPH from those who may be suffering from other disorders from their presentation.

5.2.3 Discussion

Idiopathic NPH tends to occur in patients above 65 years of age as compared to those with secondary NPH who are younger. Response to shunting seems to be worse (30–50%) for

patients with the idiopathic form than for patients with a known cause of communicating hydrocephalus (50–70%) (Vanneste, Augustijn, Dirven et al, 1992, Vanneste. 1994). Patients with the classical triad of symptoms respond better to shunting and gait symptoms generally improve more following shunting than memory followed by the urinary symptoms. These findings are consistent in this study.

Over an 18 month period 44 patients were referred to the neurosurgical unit with a clinical and radiological suspicion of NPH. Of these four patients were excluded from the study as they did not have the features of normal pressure hydrocephalus and had another pathological cause for their presentation. The details of these patients are described in detail in section 4.2.2. The mean age of the 40 patients was 76 years, similar for male (N= 15, mean age 77 years) and female (N=25, mean age 75 years). As compared to most other series there were more females (60%). In total 85% of patients were above the age of 65 years and 50% of the patients were between the ages of 76-85 years and 50% of these were shunted. Proportionately 10 patients (43%) between the ages of 65 and 75 years were shunted. The older the patients and the longer the duration of their symptoms coupled with co-morbid factors the less likely they improve. Patients with age above 65 showed improvement similar to those below 65 years in this study. In the present study no correlation was found between patient age and outcome following treatment at 1 year. The lack of a direct relationship between age and improvement after surgery in this study is consistent with other study data revealing no relationship between age and outcome (Black, 1980, Larsson, Wikkelso, Bilting, et al, 1991, Thomsen, Borgese, Bruhn, et al, 1986, Stambrook, Cardoso, Hawryluk, et al, 1988).

Unlike iNPH, secondary normal pressure hydrocephalus can present at any age, usually younger age and they have a better outcome to shunting. The mean age was not very different,

75.6 years and 71.6 years for the iNPH and sNPH groups respectively. Thirty four patients (85%) had idiopathic and 6 patients (15%) had secondary NPH. Interestingly, only 2 (9%) sNPH patients were shunted and both were females. There was one patient who was found to be an outlier regarding age (45 years) who is discussed in this section. This patient had a large right parietal AVM, which was operated on twice when he was 27 years of age (18 years prior to presentation). After his second operation he was left with left sided weakness. He presented with a 12 to 24 months history of progressive worsening of power in his right leg along with memory and urinary symptoms. He also had a large bone defect on the right hand side from previous surgery. The scalp was sunken on that side although it became fuller over the course of 12 months. He did not have any symptoms of raised intracranial pressure. His Rcsf was -1mmHg/ml/min. With infusion of saline during the lumbar infusion test he had some headache and fullness of the defect. Although the value of Rcsf in his case may not be valuable because of the loss of integrity of the skull vault, he did not show any improvement with the lumbar drainage of CSF and he was not shunted.

At presentation, 32 patients (80%) manifested with the complete clinical triad. All patients presented with gait symptoms, 85% as their first onset symptom and 57% with memory as their second symptom. Six patients (15%) did not have any urinary disturbances. Only 53% of those who presented with the classical triad were shunted of which 70% improved. There was a noticeable difference in the clock drawing ($p<0.034$) and 360-degree gait ($p<0.027$) tests between those who had the classical triad and those who didn't. Overall it was not possible to predict those who would do better with the shunt operation from the clinical presentation.

An independent samples t-test showed no significant difference between the shunted and the non-shunted patients concerning the length of their symptoms. In the literature patients with

shorter duration of symptoms showed better improvement following shunting compared to those with longer duration of symptoms. Contrary to this view, gait symptoms were of longer duration in the shunted and non-shunted groups. Interestingly the classical triad was found in 80% of the patients and 95% had gait and cognitive symptoms. These symptoms were self-reported and family members were present during the interviews for reliability of information.

Depression could affect the performance of the neuropsychological tests, and severely depressed patients were referred to the psychiatrist first for treatment. There was no difference between the shunted and non-shunted groups in their depression scores. There was one patient in each group who had medical treatment for depression before they were included in the study.

Cerebrovascular disease (CVD) is an important predictor of poor outcome (Krauss, Droste, Vach, et al, 1996, Larsson, Wikkelsö, Bilting, et al, 1991). In the Dutch NPH study patients with CVD are mostly aged above 74 with a high prevalence of arterial hypertension, diabetes mellitus, cardiac disease and peripheral vascular disease (Boon, Tans, Delwel et al, 1999). These risk factors were found significantly more often among patients with NPH than among controls (Casmiro, D'Alessandro, Cacciatore, et al 1989, Krauss, Regel, Vach, et al 1996) and the evidence of cerebrovascular disease such as white matter hypodense lesions and infarcts on CT scanning were noted in this group of patients (Kristensen, Malm, Fagerlund, et al 1996). Both of these are unfavorable outcomes after shunting. The causal relationship between CVD and NPH is unresolved but a correlation with poor outcome is clear. The neurological decline sometimes seen a few years after shunting may be due to progression of these co-morbid factors. Malm, Kristensen, Stegmayr et al in 2000 noticed a decline from 63% to 26% at 3 years. However, patient selection for shunt surgery in our study has been in the same manner as for any

neurosurgical procedure considering age, related risks and benefits. There was no correlation between poor outcome and CVD or hypertension in this study.

5.2.4 Summary

A detailed assessment of the clinical features and demographics of the patients in the study failed to show any correlation between age, etiology, presentation, duration of symptoms, co-morbid factors and the outcome following shunting. There were more patients with the classical triad and they showed better improvement in the clock drawing and 360-degree turn test compared to those who did not have the classical triad.

5.3 Radiological Evaluation

5.3.1 Introduction

Radiological evaluation not only helps in diagnosis but also in the differentiation from other conditions that may mimic NPH and to identify those who may be having evidence of cerebrovascular disease (CVD) and ischemia. In this section the usefulness of a CT scan in correlating the radiological improvement to clinical improvement is discussed.

5.3.2 Aim 2

To evaluate the usefulness of the CT scan in identifying and preventing complications and predicting outcome at 1 year between the shunted and the non-shunted patients.

5.3.3 Discussion

Radiological evaluation on its own has little significance, but coupled with classical clinical features it has a high prognostic index of surgical success. CT scans are used to evaluate the prognosis of the condition following treatment. The Evans' index is not an appropriate measure of changes in ventricular size among different individuals. Instead, determining the EI is

a proven method to monitor changes in the ventricular size following shunt placement in an individual patient, regardless of whether the size of the ventricles decreases or not. The reduction in the Evans' index was classified as significant (0.12), moderate improvement (0.06 to 0.11) and no reduction (0.05) in ventricular volume. There was no significant difference between the groups in the baseline Evans' index. Volumetric measurements may be helpful in clinical assessment postoperatively and in guiding programmable valve pressure settings (Anderson et al, 2002). No study in the literature has shown evidence of a positive association with any of the imaging criteria with clinical improvement except a recent study by Marmarou, Young, Aygok et al. 2005. They showed a reduction in ventricular size at 1 year which was statistically significant ($p<0.001$).

In this study, of the 23 patients who were shunted, the Evans' index was compared at base line and at 1-year post shunt. Of the 52.5% of those who showed moderate reduction in the ventricular size, 50% had clinical improvement, 33% did not improve and 16.6% had deteriorated. Amongst the 43.5% of patients who had no postoperative change in Evans' index all patients showed clinical improvement and only one (4%) patient showed significant reduction in the ventricular volume associated with clinical improvement at 1 year. The mean changes at baseline and at 1 year were statistically significant ($p<0.001$), and better clinical outcomes were observed in patients in the shunted group with little or no alteration in ventricular size patients. Similar conclusion was reported by Meier, Paris, Grawe et al, 2003. Reduced compliance seemed to be the best predictor of rapid and marked reduction in ventricular size (Tans and Poortvlie, 1989). There was also a suggestion that reduction of ventricular size following CSF shunting is not exclusively related to CSF dynamics and more likely to depend upon the intrinsic elastic properties of the cerebral parenchyma, which vary with age and/or co-existing pathologies

in the brain (Tans and Poortvliet, 1988). Others argue that unless not assessed volumetrically, changes of the ventricles may go undetected, questioning any statement about the significance of ventricular changes after shunting observed in NPH patients (Kitagaki, Mori, Ishii et al, 1998).

Comparing the periventricular changes at baseline and 1 year, 5 (55%) out of the 9 patients who had periventricular changes were shunted. These changes improved significantly in 4 patients. Although the correlation of periventricular changes with clinical outcome is not clear from the literature, our patients show good radiological and clinical improvement. Of the 6 patients who had cerebral infarcts 2 patients were shunted and both did not show any clinical or radiological improvement. Two patients who were not shunted showed new periventricular changes and a further 2 developed ischemic changes at 1 year follow up. One of these 2 patients developed a left sided stoke which completely resolved clinically at 1 year. Those with previous cerebral infarcts can progress with shunting although this was seen in only 1 patient.

Nevertheless, CT measurements of ventricular width and the “so called” periventricular edema has shown a variable change after shunting (Tans and Poortvliet, 1988) and was not supposed to play any role for the clinical outcome, particularly in idiopathic NPH. Most crucial, however, is the accurate selection of those patients which may benefit from shunting based on both the clinical and imaging findings. In a retrospective analysis of imaging and clinical findings Vanneste, Augustijn, Tan et al, 1993, were the first to introduce a definition of NPH classified using the terms "probable", "possible" and "unlikely". This was based on an ordinal global scale derived from combined clinical and CT data, which predicted the clinical outcome in 112 patients shunted for presumed normal pressure hydrocephalus (NPH). Based on CT characteristics they achieved sensitivity values of 46% and specificity of 91% in the probable

shunt responder group of 17 patients. The best strategy was to shunt only patients with "probable shunt-responsive NPH" providing "typical CT and clinical findings" with a positive predictive value (PPV) of 65%. However, the positive predictive value of the possible shunt responders group was only 24%. Surprisingly, these data were supported by a more recent analysis made by Boon et al, 2000, suggesting that best predictive rates based on a combination of "typical" clinical and imaging findings may not exceed 60%. This clearly shows that the prognostic value of CT is limited on its own.

5.3.4 Summary

At 1 year 50% of those who showed moderate reduction in the ventricular size (Evans' index) had shown clinically significant improvement. Although the numbers are too small (5 patients-55%), to do any statistical tests, it is clear that those who had periventricular changes prior to shunting showed both clinical and radiological improvement, whereas those with cerebral infarct (6 patients) were poor candidates for shunting. An early CT scan at 4-6 weeks was useful to identify (a) the position of the catheter (b) patients who may need a re-operation for inappropriate catheter position and (c) those who are likely to need close observation for subdural haematomas and planning shunt reprogramming. At 1 year the Evans' index showed a significant reduction ($p=0.001$) in the size of the ventricle in the shunted group and the periventricluar lucency improved radiologically in 4 out of 5 patients.

5.4 Baseline tests

5.4.1 Aim 3

To evaluate the baseline values of the screening, neuropsychological and gait tests at presentation to determine whether there were any significant differences between the shunted and the non-shunted patients. This may help to identify those who may be suitable for shunting.

5.4.2 Discussion

Although the screening tests did not discriminate specific patterns of dementia they are able to exclude, and can be used to investigate the patients who may be severely demented or severely depressed, as assessed by MMSE or BDI respectively. Patients with a very low IQ can underperform in some of the tests and the NART scores were used to evaluate this. The NART and BDI were not performed during the follow-up reviews at 6 and 12 months. These screening tests are not diagnostic nor are they equivalent to a neurological examination or formal mental status testing. NART test for premorbid IQ showed similar means between the shunted and non-shunted patients and more than 92.5% of the patients had normal intelligence. Five (12.5%) patients were moderately and two (5%) patients were severely depressed. Both patients with severe depression were treated with anti-depressants initially. One of them was shunted and showed improvement at 6 months but not at 1 year. This concurs with other studies where patients with severe depression were poor candidates for successful shunting.

The dementia of NPH is thought to be sub cortical and mild to moderate with 78% of patients having a normal to moderate dementia. MMSE is not always sensitive in picking up early dementia. Cognitive performance varies by age and educational level and there is an inverse relationship between MMSE scores and age in this study. Once the limitations of the test are understood, it can be very helpful in both the diagnosis of dementia and in monitoring the

response to treatment. Some studies have shown poor outcome from shunting with patients with severe dementia. Nine patients had a MMSE score of less than 13 (severe cognitive deficits). Five of these patients were shunted, three showed improvement at 1 year and two of them had no improvement at all. Four of those who were not shunted did not show any improvement and two of them deteriorated at 1 year. This study does not confirm a worse outcome after shunting in those with severe dementia.

Reports of neurocognitive response to shunting have been variable and studies that predict cognitive outcomes after shunting are limited. As NPH progresses, cognitive impairment may become more generalized and more refractory to treatment. Nevertheless, even patients with fairly advanced dementia may still respond positively to shunting as shown in this study with 3 of the 5 patients shunted with severe dementia showing improvement. The baseline neuropsychological tests showed no significant differences between the shunted and the non-shunted patients at presentation. The Pearson correlation did not show a relation between the neuropsychological and gait tests.

5.4.3 Summary

The screening tests used in the study did not discriminate between the shunted and non-shunted patients. Both groups had a normal IQ on the NART tests and 82.5% patients had a mild to normal BDI. 77.5% patients had mild to moderate cognitive deficits in the MMSE scores. There was no difference in the baseline neuropsychological and gait tests between the two groups.

5.5 CSF hydrodynamics

5.5.1 Aim 4

To evaluate the usefulness of Rcsf value as a criterion for shunting and analyse the outcome of the patients shunted with an Rcsf of 12mmHg/ml/min or more.

5.5.2 Discussion

The constant pressure infusion methods generate more data during a given time period than by using a constant flow infusion. The disadvantages are the more invasive nature of the procedure (two punctures of the CSF space) and the more complicated equipment required. In this study the simple lumbar constant flow infusion with one infusion rate was used, which has proved to be a reliable and reproducible method.

Both lumbar infusion studies and ELD predict a positive outcome of shunt operations. They are complimentary to each other and best used together for optimal patient selection. There is also the argument that merely recording the steady state plateau pressure during the constant lumbar infusion study as originally described by Katzman was more accurate than calculating the Rcsf values. This is because if a patient had a high opening pressure at LP, the difference between the plateau pressure and the opening pressure will be low and vice versa. This high opening pressure will tend to disqualify patients from shunt surgery and vice versa if low (Kohlon, Sundborg, Rehncrona. 2002). Although good-to-excellent results were obtained using Rcsf as a predictor of outcome (Børgesen and Gjerris, 1982, Hartmann and Alberti, 1977, Lamas and Lobato, 1979, Lundar and Nones, 1990, Nelson and Goodman, 1971, Price, 1989, Tans, 1979, Tans and Poortvliet, 1984, Tans and Poortvliet, 1985, Boon, Tans, Delwel et al. 1997), an equal number of studies has shown a less favorable predictive value (Wolinsky, Barnes, Margolis et al, 1973, Stein, Langfitt et al, 1974, Malm, Kristensen, Fagerlund et al, 1995, Janny,

Colnet, Veyre et al, 1981, Kosteljanetz, Nehen, Kaalund et al, 1990, Graff-Radford, Godersky, Jones et al, 1989, Delwel, de Jong, Avezaat et al, 1989). Another limitation of this test is that it needs a dedicated specialist who is able to perform and interpret the results.

Although an Rcsf of 12mmHg/ml/min was used as one of the positive predictors in this series, the objective was also to determine the positive and negative predictive values of different ranges of Rcsf. At cutoff value 12 mm Hg/ml/minute, positive predictive values for improvement were approximately 68%, but the likelihood ratios were low. The likelihood ratio rose to 1.38, with a positive predictive value of 80%, for an Rcsf of 18 mm Hg/ml/minute. The negative predictive values were disappointingly low for all levels of Rcsf. In some studies (Delwel, de Jong, Avezaat et al, 1989) Rcsf was used as a criterion for the diagnosis of NPH. Price emphasized the importance of different cutoff levels of Rcsf in 1989. The proportion of his patients responding positively to shunt placement increased almost linearly with increasing Rcsf. In the shunted group 17.5% patients improved with Rcsf values less than 12 and all of these patients showed improvement following ELD. If we had used Rcsf of 18mmHg/ml/min as a cutoff criterion, 4 patients who improved with an Rcsf between 12 and 18 may have been left out. The explanation for those who improved with low Rcsf could be due to physiological variability and more importantly was the improvement following ELD. Boon et al, 1997 demonstrated that leakage around the needle during an infusion test could explain this, although we cannot confirm this in this study. More important are the patients who did not improve despite the high Rcsf values; this cannot be explained.

At an Rcsf of >12mmHg/ml/min there were significant differences between the shunted and the non-shunted groups in all the neuropsychological tests and most of the gait tests except the 10 metre walking test.

5.5.3 Summary

It can be concluded that the Rcsf value of 12mmHg/ml/min was valuable in shunt selection but it should not be used as a positive indicator by itself, but instead used in combination with clinical as well as radiological findings typical for NPH and improvement following ELD. This study cannot recommend that choosing a higher Rcsf as a cut off was more valuable than using an Rcsf of 12 mmHg/ml/min in shunt selection.

5.6 Response to ELD

5.6.1 Aim 5

To determine whether the effects of external lumbar drain (ELD) on supplemental neuropsychological and gait tests in addition to urinary symptoms would identify those patients who would benefit from a shunt, and to determine if there was any correlation between the tests used to select patients for shunting at 1 year.

5.6.2 Discussion

5.6.2.1 Introduction of selection bias

Based on the improvement following ELD patients were classified into probable, possible and unlikely groups. Significant improvements ($p<0.05$) were seen for all of the neuropsychological tests and most of the gait tests except the 10 metre walking time and 360 degree turning time in the shunted patients. Clearly this approach introduces a selection bias at this stage. Patients are put in the respective categories based on their results and treatment is instituted on this basis. The alternative is to shunt all patients in the study irrespective of the ELD outcome as in the Dutch NPH study (Boon, Tans, Delwel et al, 1998), but there are ethical considerations to be taken into account with this approach. Since this bias is unavoidable in the

study more emphasis will be given to the group of patients who were shunted and to look at those who improved versus those who did not improve. This will be discussed more in detail in chapter 6.6.

5.6.2.2 ELD outcome

Studies by other investigators who used ELD vary in their results. Walechenbach, Geiger, Thomeer et al, 2002, reported a positive predictive accuracy of 87% with ELD and a negative predictive accuracy of 36% in 43 patients with iNPH and justified shunting patients who improved with ELD. They also concluded that those who did not improve should also be shunted given that 4 out of the 18 patients in their series improved despite negative ELD. This conclusion cannot be justified. Haan and Thomeer, 1988, in a retrospective study of 32 patients showed 10 patients to improve with a lumbar tap test and the 22 patients who did not improve underwent ELD and all of them showed improvement and were shunted. They concluded that ELD was a safe and effective means of predicting improvement.

5.6.2.3 Within shunted patient discussion

It is very important to discuss the patients within the shunted group in the probable and possible category. Eleven out of 12 (30%) patients in the probable group were shunted and twelve of the 19 patients in the possible group were shunted. Nine patients did not improve with ELD and none of them were shunted. There was a 74% improvement seen at 1 year in those patients who underwent shunting following improvement from ELD in the probable and possible group. Seventeen percent did not show any improvement and 9% worsened following shunting. In the probable group 73% improved, 18% did not improve and 9% were worse. The one patient who refused to have a shunt did not improve. In the possible group, of the 12 patients who were shunted 75% improved, 17% did not improve and 8% were worse. In the non-shunted group of 7

patients, 14% improved with no treatment, 14% did not improve and 72% worsened. Based on the patients in the possible group, if we used the 7 patients in this group who refused a shunt as controls, 72% of the non-shunted patients deteriorated with observation at 1 year. On the other hand those 75% of patients in the same group who were shunted had a significant improvement. We can conclude from this that the ELD was a significant test to assess the outcome of treatment.

5.6.2.4 ELD retesting

The natural history of NPH shows that most patients will continue to get worse while a significant number will remain stable after a period of decline (Marmarou, Young, Aygok et al, 2005). There are no predicting factors to identify those who will remain stable or get worse. Some clues are the severity of dementia at presentation, associated co-morbidity and presence of Alzheimer's disease. There are few factors that can provide false negative results on the ELD and Rcsf calculation including the position of catheter and patient co-operation during the tests. Other factors that may introduce false negative results are lower back pain and discomfort in performing the tests following the lumbar puncture, post drainage headache and unsteadiness and environmental factors. Repeating the ELD test on a separate occasion may alleviate these factors and give a true positive result. Those who continue to get worse can either be watched or retested. Although all 14 patients who deteriorated at 6 months were offered a retest only 2 patients accepted this. There are several reasons for this. The majority of the patients did not want to undergo a further stay in hospital, receive a lumbar puncture and drain again and have all the tests repeated. Whether using a smaller LP needle could have changed the experience needs to be considered for future studies.

5.6.3 Summary

Of the 31 (77.5%) patients (probable and possible group) who were candidates suitable for a shunt only 23 got shunted and at 1 year only 17 (74%) of these improved in their clinical symptoms. Nine of those who were not suitable following an ELD did not get shunted and as expected none of them improved after a 1-year period of conservative management. Supplemental tests used to identify the response to ELD were useful to categorise patients for shunt selection. These categories were able to identify a high percentage of patients who may respond to a shunt. Although the groups were highly selected from the criteria chosen, those patients who did not receive a shunt can be used as a control group to predict the natural history of the disease. Of those not responding to ELD 29% remained stable and 66% progressively deteriorated over a period of 1 year.

5.7 Outcome of surgery at 6 months and 1 year

5.7.1 Introduction

In this section aims 6 to 8 are discussed. The outcomes of the shunted and non-shunted patients are discussed at 1 year. Tests that may help identify patients who may respond better to shunting are also discussed.

5.7.2 Aims 6 to 8

Aim 6

To examine the effects of shunting to determine whether the symptoms of NPH improve following surgery. The control group (those not receiving a shunt) were reassessed after the same time period to determine which factors alter over time.

Aim 7

To compare the selection criteria including ELD, Rcsf values and outcome of the shunted patients who have responded well to surgery, with those who show little or no improvement. Within group analysis may assist in developing criteria, in the future, to select patients who are most likely to benefit from surgery.

Aim 8

To investigate if any of the neuropsychological or gait tests at baseline were able to predict surgical success or failure in the shunt improved patients at 1 year.

5.7.3 Discussion

Only a few papers report an extended follow-up of patients with NPH and the value of the supplemental tests. All patients were followed up to 1 year. The non-shunted controls were also followed up with clinical and radiological review.

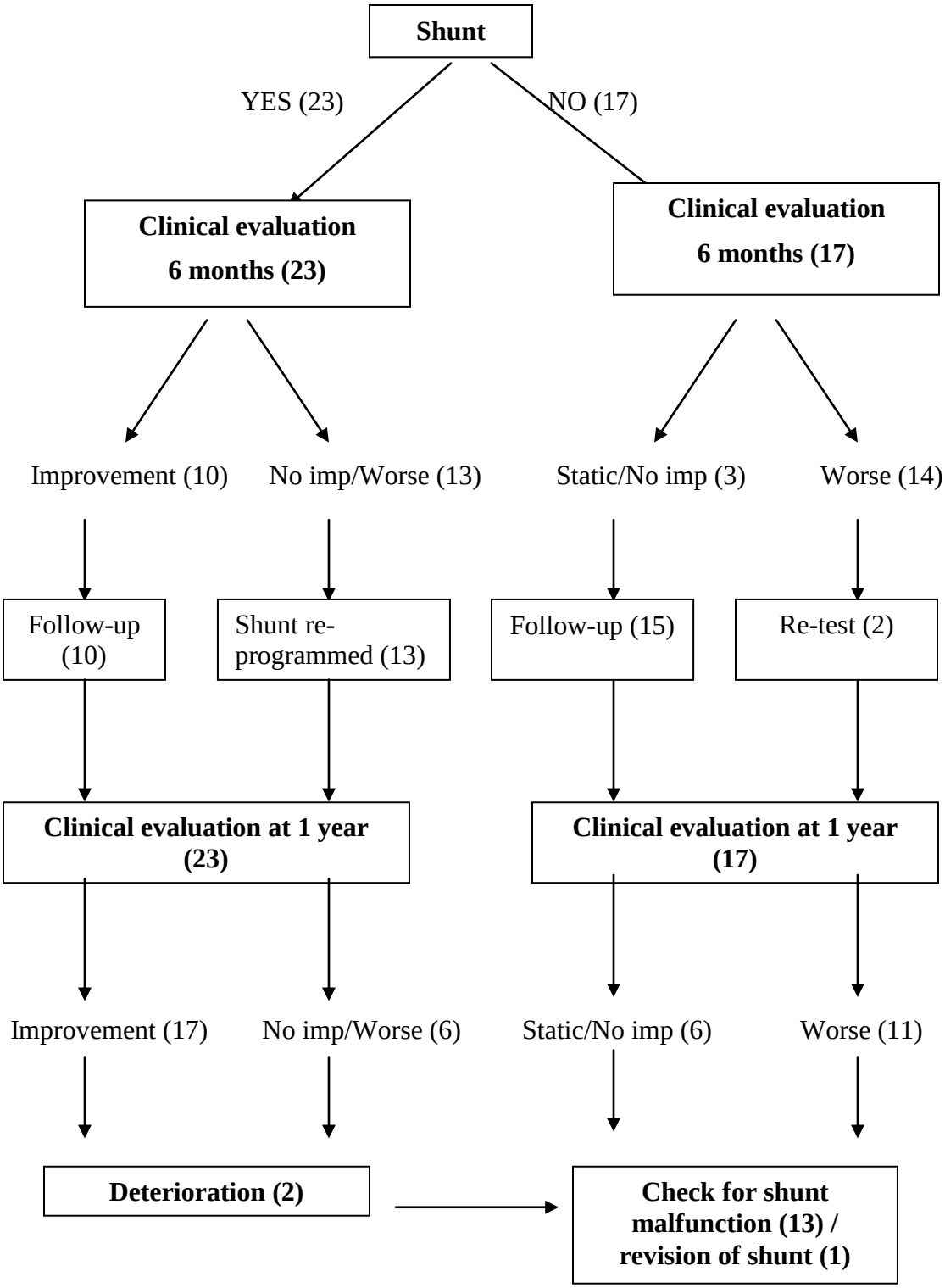
There were significant differences between the shunted and the non-shunted patients in all the neuropsychological and most gait tests at 1 year. The improvement was more marked at 1 year compared to 6 months. Overall there was a 74% improvement in the shunted patients and 9% got worse. In those who were not shunted, as expected, there was deterioration in about 65% of patients and about 30% remained stable. Over time 17% of non-shunted patients showed a slight improvement in their condition without any treatment. There were more patients who improved or remained stable than those who got worse in the non-treated group.

Gait is generally believed to improve most with treatment (Graff-Radford and Godersky, 1987). Only 26% improved in their urinary symptoms. Some previous studies report that only a very small percentage of patients show improvement in cognitive function. In this study 83% of patients showed improvement in their gait symptoms and 78% of patients showed improvement in memory at 1 year as supported by Meier, Zeilinger and Kitzel, 1996, who found higher rates of improvement following shunt surgery, of 65% at short term follow up. Other studies have shown mild regression at long term follow-up with only 54% remaining improved (Thomas, McGirt, Woodworth et al, 2005). Only 26% of the patients improved in their urinary symptoms. No statistically significant association was found between symptom duration and outcome. The overall improvement of the shunted patients was 43% at 6 months and 74% at 1 year. The significant improvement at 1 year compared to 6 months is due to the change in the shunt pressure setting during this period.

5.7.4 Shunted vs non-shunted patients

Figure 5.4 shows the flow chart of the patients in the study. The chart explains at each stage the total number of patients involved following treatment. Of the 23 shunted patients 13 did not improve and they all had their shunt re-programmed. At 1 year review 7 of these 13 patients improved with shunt re-programming and 6 of them had no improvement. In the non-shunted patients at 6 months only 3 patients were static and 14 patients deteriorated. Retest was offered to all 14 patients but only 2 accepted. Unfortunately both did not improve and were continued to be followed up. At 1 year interestingly 3 more patients slightly improved in the non-shunted group. These details were discussed in the previous chapter 5.6.

Figure 5.4: Flow chart of follow-up including number of patients.



Because the shunted and non-shunted patients are highly selected, the best way is to compare the two groups separately. Within the shunted group the patients who improved with surgery were compared with those who did not improve following a shunt to identify factors that help to guide selecting patients for shunting in the future. Assessment tools are both invasive (lumbar puncture and ELD) and non-invasive (Neuropsychological and gait tests). Invasive tests carry a small but serious risk of meningitis. If the non-invasive tests were able to predict better those who will respond to a shunt it will help avoid performing the invasive tests. But this is not possible as the baseline neuropsychological and gait tests failed to show a pattern to guide patient selection. Hence a lumbar puncture to calculate the Rcsf and ELD is necessary to quantitatively assess improvement in the neuropsychological and gait tests. MMSE and the 10 metre walking tests were good predictors of surgical success. MMSE is used as a screening test to assess various components of dementia and in clinical practice this is a quick way to assess improvement following a lumbar puncture. Regression analysis showed that the verbal fluency test for FAS was the only variable that was important.

5.7.5 Rcsf as a selection criteria in shunted patients

An Rcsf of 12mmHg/ml/min was used as a criterion for treatment. As discussed in Table 4.21 seven patients with an Rcsf of < 12 mmHg/ml/min and 16 patients with an Rcsf > 12 mmHg/ml/min were shunted. Six of these had an Rcsf of between 12 and 18 mmHg/ml/min and 10 had an Rcsf of > 18 mmHg/ml/min. Of those shunted with an Rcsf of > 12 mmHg/ml/min, 75% improved at 1 year. Interestingly all patients with an Rcsf of < 12 mmHg/ml/min (100%) improved with a shunt. This shows that although choosing an Rcsf cut-off value can be a positive prognostic indicator it should be supplemented with improvement following ELD. A similar conclusion about the usefulness of Rcsf values was drawn by several studies. (Malm, Kristensen,

Fagerlund et al, 1995, Janny, Colnet, Veyre et al, 1981, Kosteljanetz, Nehen and Kaalund, 1990, Graff-Radford, Godersky and Jones, 1989, Delwel, de Jong, Avezaat et al, 1989).

5.7.6 ELD and outcome of shunted patients

Following the criteria used in Table 3.3, 30% of patients in the "probable" group improved following ELD. All but 1 patient was shunted. Of these patients 73% improved at 1 year. Twelve patients out of 19 in the "possible" group were shunted and 63% of these patients improved. None of the patients in the unlikely group were shunted. Considering the patients in the probable and possible group would improve with a shunt, 74% showed improvement at 1 year, 17% showed no improvement and only 9% were worse. This confirms that classifying patients following ELD into "probable", "possible" and "unlikely" has serious benefits in identifying those who are likely to benefit from a shunt.

5.7.7 Summary

At one year there was a statistically significant difference between the shunted and the non-shunted patients in their neuropsychological and gait tests. The improvement was noticed more in the gait than neuropsychological tests followed by a smaller improvement in the urinary symptoms. Except the urinary symptoms there was a sustained improvement in the clinical symptoms over time from 6 months to 1 year. The MMSE and 10 metre walking tests were good predictors of surgical success and a regression analysis showed VF to be a good prognosticator of outcome. Baseline tests could not differentiate those who will respond to a shunt and invasive tests (LP and ELD) will be needed to identify these patients. Using Rcsf on its own was not useful and classifying patients based in outcome from ELD was helpful in making a treatment decision.

5.8 Complications of ELD and shunting

5.8.1 Aim 9

To identify the complications occurring from external lumbar drain, shunt and use of anticoagulants.

5.8.2 Discussion

The complications following lumbar puncture and insertion of ELD were minimal. Two patients (5%) developed symptoms and signs of meningitis. One of these patients had grown staphylococcus aureus in the CSF culture and later on had a shunt insertion after 2 months, and the other did not qualify for shunting. In the literature, the risk of meningitis from a spinal catheter following neurosurgical post-operative drainage of CSF is 4 – 10%; however this may not reflect the rate in NPH population. Mortality is quoted at 1-2% in some series. Three patients (7.5%) had their lumbar drain disconnected from the lumbar CSF space and a repeat ELD insertion was performed. The way dressings were applied to secure the lumbar drain was modified during the later part of the study and this complication was avoided. Two patients (5%) developed low pressure headaches and needed fluid hydration and pain killer for more than 24 hours following ELD. No other complications were noted following the lumbar puncture and ELD.

The incidence of co-morbidity plays a role in determining the risk to benefit ratio. Complications of shunting can occur at the time of shunt operation or after the procedure which may be immediate or delayed. The most common immediate complication reported is intracerebral haematoma, 3% in the Dutch series (Boon, Tans, Delwel et al, 1998). Delayed complications normally are infection, seizures, shunt malfunction, under and over drainage, headaches and most importantly subdural collections. The incidence of subdural collections

quoted in literature is 2-17% (Black, 1980) and 9.5% in iNPH and 1.4% of Secondary NPH (Zemack and Romner, 2002). In the Dutch Normal-Pressure Hydrocephalus Study routine CT screening after VPS insertion showed subdural effusions in 71% of patients with low-pressure valves and in only 34% of patients with medium-pressure shunt systems. The subdural collections can either be a simple effusion, which can be observed with close surveillance or a major haematoma requiring immediate drainage. Early drainage of asymptomatic subdural effusions has not shown any superior benefits than conservative management. Early CT scanning may pick up these collections from 4-6weeks following surgery. Adjustable valves are useful in the conservative management of subdural collections by increasing the opening pressure and prevent worsening. Mortality related directly to shunt insertion is very low but the risk increases gradually over time after shunting when complications arise (Malm, Kristensen, Stegmayr et al, 2000). Patients on anticoagulants did not pose an excess risk of bleeding problems. There was no mortality in this study at 1 year follow up.

5.8.3 Summary

The risk of subdural haemaetoma and hygroma was significantly reduced in the later part of the study by the way in which the patient's shunts were programmed. The risk following ELD was minimal and the technique of securing the drain to avoid the displacement was modified. Recognized complications of shunt placement like inadequate position, over and under drainage related complications as reported in other series were seen. There was neither mortality nor shunt infection in our series.

5.9. Value of programmable shunt

5.9.1 Aim 10

To identify the value of using a programmable shunt.

5.9.2 Discussion

Various strategies for setting the opening pressure and making the adjustment have been mentioned. Some have used a high initial opening pressure that can be decreased until there is an improvement of symptoms (Pollack, Albrigh, Adelson et al, 1999) whereby others recommend a low opening pressure that is increased in the postoperative period (Turner and McGeachie, 1988). A third option would be to start with a reasonably high setting at the time of shunt insertion, reduce the opening pressure to a level at which the brain parenchyma gives way to ventricular shrinkage, and then increase the pressure slightly once the clinical symptoms begin to improve to avoid complications of over drainage (Hakim, Hakim, Hakim et al, 2001). In the initial part of the study the shunt pressure was set at the opening pressure at lumbar puncture. It was found that 5 (38%) of the 7 patients who developed SDHy and SDH had shunt valve settings set between 60-90mm H_2O. After these complications were encountered, during the later part of the study the opening pressure of the valve was set at 130 mm H_2O and gradually reduced at their first visit if there was no evidence of SDHy or SDH. The incidence of SDHy and SDH significantly reduced, although 2 patients presented at 1 year with a SDHy and SDH not needing any surgical treatment.

The first 13 patients had their shunt pressure set at the opening pressure during the lumbar puncture. There were 5 (38%) patients who developed complications of subdural haemetoma and hygroma. Two had a haemetoma and one needed a burrhole drainage of the

blood collection and the other was managed conservatively by raising the pressure to 130 mm H_2O. It was found that they did not improve following the raise in pressure and their pressures were slowly lowered. Following this observation the policy of shunt programming was changed in the later part of the study and the pressure was set at 130 mm H_2O and then lowered during their follow-up starting from 4-6 weeks. Of the 10 patients in this group 1 (10%) patient developed a subdural collection with a minimal pressure and the other patient develped a subdural hygroma. A burrhole evacuation of the clot was performed on the subdural patient. There was certainly a 28% reduction in the number of subdural formation following this change in pressure setting at the time of shunt insertion.

Adjustments were performed mostly at the time of first review at 4-6 weeks; the valve was re-programmed by lowering the pressure by 20 mm H_2O. If there were signs of overdrainage then the pressure was raised by 20 mm H2O. A check X-ray was taken to confirm every change. Everytime a patient had a change to their programme they were reviewed within 4 weeks to see the effect of change and further adjustments were made if necessary. The other reasons for the change in the pressure was performed when there was evidence of a subdural hygroma (SDHy) or subdural haematoma (SDH) on CT scans at 4-6 weeks post surgery. The patients were not seen on a regular basis as recommended in some series for change of pressure. The patient, family and carers were well instructed to contact us if there was either deterioration or no improvement in their clinical condition. The patients were given a card that described the pressure setting in their valve.

5.9.3 Summary

The results show that the best way to set the opening pressure of the programmable valve was to set at a higher pressure and then gradually reduce if the CT scan did not show any

evidence of SDHy and SDH. The incidence of SDH and SDHy reduced with this policy. The average change of the programmable shunt was less with the starting at a lower pressure than at a higher pressure, which brings the argument of using low pressure differential pressure valve. Radiological findings were not evaluated after each adjustment, because the change in ventricular size, in our experience, does not always correlate with the clinical outcome. Programmable valves help in adjusting the pressure of the shunt and also in treating patients with subdural conservatively.

Chapter 6: Conclusions

6.1 Value of clinical and radiological criteria

Analysis of the data in the literature shows some positive prognostic indicators with the complete clinical triad (Benzel, 1994, Raftopoulos, Deleval, Chaskis et al, 1994, Black, 1980, Jacobs, Conti, Kinkel WR et al, 1976), recent onset of symptoms (Caruso, Cervoni, Vitale et al, 1997, Graff-Radford and Godersky, 1986, Larsson, Wikkelso, Bilting et al, 1991, Thomsen, Borgesen, Bruhn et al, 1986, Peterse, Mokri, Laws et al, 1985, Wood, Bartlet, James et al, 1974), a history of gait abnormality before dementia (Caruso, Cervoni, Vitale et al, 1997, Graff-Radford and Godersky, 1986, Graff-Radford, Godersky, Jones et al, 1989), small cortical sulci (Benzel, 1994, Black, 1980, Tans, 1979), enlarged temporal horns (Stambrook, Cardoso, Hawryluk et al, 1988, Tans, 1979, Wikkelso, Andersson, Blomstrand et al, 1989), secondary NPH (Larsson, Wikkelso, Bilting et al, 1991, Thomsen, Borgesen, Bruhn et al, 1986) and the absence of other contributing causes of dementia.

In this study age, etiology, presentation, duration of symptoms and presence of co-morbid factors were unrelated to outcome. Evans' index showed a significant reduction in the size of the ventricle in the shunted patients at 1 year.

6.2 Value of supplemental tests

After confirming a clinical and radiological diagnosis the decision to shunt a patient was based on responses to the supplemental tests. These tests can increase the predictive accuracy for prognosis to greater than 90% (Marmarou, Bergsneider, Klinge et al, 2005). Screening tests used in this study were able to differentiate patients with depression and severe dementia. From the

MMSE test, 77% of patients suffered mild to moderate dementia of NPH type. There were no significant differences between the shunted and the non-shunted patient's baseline neuropsychological or gait tests. A multiple regression analysis showed the verbal fluency-FAS to be the only test to predict a good outcome in the shunted patients at 1 year.

Rcsf testing and improvement to ELD are known to correlate with good outcome in several series as mentioned previously. The range of better outcomes mentioned lies between 12 and 18 mmHg/ml/min. Sixty three percent of patients had shown improvement at 1 year with an Rcsf of more than 12mmHg/ml/min. The post-test probability of having shunt response was 68% and the negative predictive value was 14% with a specificity 64% and sensitivity of 16%. The specificity increased with rising Rcsf values.

Thirty one patients (77%) were likely to improve with shunting in this series (probable and possible group). Twenty three (74%) of these patients were shunted and 18 (58%) showed improvement at 1 year. The sensitivity of ELD was 100% and the specificity was 52% with a PPV of 74% and a NPV of 100%. This shows that both Rcsf testing and ELD enhance a positive predictive outcome of shunt operation. From this study the Rcsf cut off value recommended is 12 mmHg/ml/min as 4 patients who showed improvement at 1 year may not have been shunted if the Rcsf cut off was raised to 18 mmHg/ml/min even though the specificity and PPV may rise.

6.3 Value of shunting and pressure setting

The Cochrane review concluded that "there is no evidence to indicate whether placement of a shunt is effective in the management of NPH" (Esmonde and Cooke, 2002). Recent international guidelines recommend CSF diversion for iNPH patients in whom there is a favourable risk-benefit ratio (Marvin, Black, Klinge et al, 2005). The lack of a randomised

controlled trial gives rise to discrepancy in the views. There are approximately 162 different companies making valves in the world market as of 2006. Of these 137 are simple differential valves and 118 advanced technology valves (26 adjustable pressure valves). Unfortunately there no data comparing superiority of one valve over the other in NPH (Drake, Kestle, Milner et al, 1998). Data from the UK shunt registry, over a period of 8 years, shows the 1-year revision rate for overdrainage to be 0.9 +/- 0.8% (SD) in NPH by using various shunts, almost invariably due to subdural collections. Hence, we can conclude that there was no significant difference between the valves systems, but, certainly the complications such as subdural haematomas and hygromas can be more readily managed with adjustable valves. Adjustable valves allow for raising or lowering the pressure differentials according to the clinical need and are now implanted as a matter of routine (Zemeck, Romner, 2002). Selecting a higher pressure at shunt implantation and gradual reduction over a period of time has reduced the complication of SDH and SDHy rates significantly. This also gives the opportunity to select the best response to pressure setting for that individual patient by repeated adjustments.

6.4 Identifying the shunt responsive patients

In this study it was found that the classification of patients into probable, possible, and unlikely categories following ELD was useful in determining the treatment. This was recommended by the recent international study group for NPH. (Relkin, Marmarou, Klinge et al 2005). Hopefully these criteria will be widely applied in clinical practice and will promote greater consistency in patient selection in future clinical investigations involving NPH. Ideally, the best way to study the selection of patients with shunt responsive NPH would be a randomised control study or to shunt all patients in the three categories, but for ethical reasons this was not possible in this study. If the risks of shunting were small, this would be an appropriate approach;

however as that is not the case; we still need diagnostic methods to select those patients who are most likely to benefit from CSF diversion.

All 23 patients who were shunted were positive to ELD, of which 17 (74%) showed improvement at 1 year. The CSF drain effectively mimics the effects of the shunt; therefore those who respond to this are most likely to respond to surgery. Those who show no improvement are less likely to benefit from a shunt.

6.5 Awareness of NPH

Current NPH research in the UK is isolated to very few dedicated centres. Even hospitals that have a dementia service do not have a multi-disciplinary team to deal with this entity. Patients without appropriate investigation may receive a shunt. These patients are not followed up long term to study the outcome. Those who are not deemed for a shunt are lost to follow up and review. Although there are several factors it is partly due to lack of awareness among the medical community in referring these patients to the appropriate physicians. Because the elderly patients have varied co-morbidity there is a lack of sub-specialist interest among surgeons to deal with these patients. Once patients are shunted, they are subject to shunt related complications which can be delayed after several years and hence they need long term follow up. Over drainage and under drainage problems can be under diagnosed and not treated appropriately.

Because of the improved health care and increased longevity patients in their 70s and 80s are now seeking an improved quality of life and are willing to accept the risks of surgery. Evidence suggests that shorter duration of symptoms is related to better outcomes, although this was not the case in this study. In the UK, currently 700,000 or one person in every 88 has dementia, incurring a yearly cost of £17 bn. By 2051 it is estimated that the figure will rise to

1,735,087, an increase of 154% (BBC, February 2007). It is estimated that about 5% of these patients may suffer from NPH. An increasing elderly population is seen in most developed countries and more needs to be done to increase the awareness of normal pressure hydrocephalus. This awareness needs to be targeted both at the public and the medical professionals in a well balanced manner as there will a large number of patients referred as a consequence. Increasing the awareness alone will be inadequate if we are not able to implement these tests systematically. The infrastructure within the NHS needs to be better developed to perform these tests as a routine in a larger scale in a multicenter setup. This will be an important aim of future work.

6.6 Limitations of the study

6.6.1 Methodological limitations

Improvement following ELD was used in selecting patients for treatment. The selection bias introduced in assessing patients' following treatment is unavoidable for several reasons. There is no gold standard test to diagnose NPH and the treatment with VP shunt cannot be justified in those with only a suspicion of the diagnosis. VP shunt carries a serious risk. This is a serious limitation in the methodology and introduces a biased group of patients.

The alternative methodological option is to shunt all the patients. Shunting all patients will give the opportunity to study those who were expected not to improve with shunt following failure to improve with ELD. This will answer the question as to why we should or shouldn't shunt those who are unlikely to improve. This method has serious ethical considerations and this approach may not be justified for the reasons discussed in the previous paragraph.

Another method would be to randomize whether patients receive a shunt. Because there is no clinical equipoise in treatment this will again be unjustifiable. There is also the risk of losing out on those who are likely to improve with ELD and may benefit from a shunt.

Given these limitations the best option was to select patients who improved with an ELD and treat them with a shunt operation, with the intention that the majority of them have a better chance of improving from a shunt compared with those who do not show any improvement with an ELD.

Patients in this study were assessed by the researcher. A multi disciplinary approach to patient assessment and treatment was a drawback of the study. This was partly due to the difficulty in setting up such a group in an NHS setting. In future this will be a serious requirement to effectively diagnose the condition.

6.6.2 Limitation of outcome measurement

The other limitations of the study are the outcome measures. There is no standard outcome measure for NPH patients like the Glasgow outcome scale (GOS) for head injury. In most studies improvement rates and outcomes after shunting have been combined. Various measures have been used in different studies, Black scale, Stein and Langfit scale for assessment of shunt outcome, Dutch NPH scale, Japanese NPH scale only to mention a few (Marmarou, Bergsneider, Klinge et al, 2005). These are not validated for the use in NPH patients. The outcome measurements need to focus on all three components of NPH and the general measures of quality of life. Assessment of the dementia component is difficult and symptoms may progress over time especially in the non-shunted patients. According to the international guidelines published in 2005 (Marmarou, Bergsneider, Klinge et al, 2005), outcome is measured by

"improvement", "no improvement" and "worse". In this study the same measures has been used through out. General QOL measurements have not been used in this study, which needs to be included in the future.

6.7 Future Consideration

6.7.1 Future consideration from this study

The patients in this study were assessed and tested by the main researcher and the supervisory consultant in the hospital before a shunt was inserted. The differential diagnosis for NPH includes a large number that are relatively commonplace in the elderly population. Multidisciplinary approaches will be necessary in the future to assess these patients. A multidisciplinary team of specialists may consist of a neurologist, neurosurgeon, psychologist, physiotherapist and psychiatrist, where indicated. Because dementia of NPH is not easy to differentiate these patients must be seen by a clinical psychologist or a neurologist. A clinical physiotherapist assessed patients in this study. Following discussions with these professionals, a decision must be reached regarding treatment.

A 16G epidural needle was used in this study. Larger bore needles can cause more discomfort to patients and there is a potential for fluid leak around the catheter during the infusion studies. A smaller gauge needle must be used in the future. The drainage of CSF was 100ml over a period of 2 days. Recent study shows that better results are achieved with more drainage of CSF up to 250ml over a period of 3 days (Marmarou, Young, Aygok et al 2005). This gives a higher specificity and sensitivity for the post procedure analysis.

Patient's life expectancy and co-morbidity should be taken into account as they determine the outcome. The current study is only a one-year follow up. This will not answer questions

regarding risk benefit ratios of shunt insertion, which are more significant after one year. A long-term follow-up is necessary. These patients should be followed up for a period of 3-5 years. The patient's managed by observation should also be followed-up in a similar manner to understand the natural history.

From this study adequate experience has been gained to recruit, organise and investigate large number of patients for appropriateness of shunting and long-term follow-up. The study is being continued and expanded. Further assessments of Cine Phase MR CSF flow studies before and after ELD and shunting, assessment of CSF biochemical markers and measurement of lumbar pressure are being undertaken currently. It is proposed to follow up the patients in this study for a period of 3-5 years to predict long term outcome. The protocol used in this study has been modified to collect more data and additional investigation as mentioned above. The experience gained and the scope of this study has expanded. It is hoped to collaborate with other centres in the North West of England and wider.

6.7.2 Future considerations in a broader context.

Since the disease is complex and there may not be a gold standard test to predict shunt response, future efforts should be directed towards better identification of the pathogenesis of idiopathic NPH. A randomised controlled trial cannot be implemented for several reasons, but this would be ideal. With the advances in diagnostic tests and shunt design, the patients outcome is significantly better and doctors in the forefront are showing a renewed interest in treating NPH across the globe. In many ways we are doing better, thanks to the 40 years of clinical studies and new investigative technology. In identifying those who will respond best to a shunt, tests revolving around lumbar puncture, lumbar tap and drainage have been used as the standard methods when assessing improvement. These are invasive tests with minimal but serious risks.

Many CSF factors have been identified that can diagnose the disease and predict the outcome. MR CSF flow studies can predict shunt responders and PET scans have been used to detect periventricular blood flow improvement post shunt. Non-invasive methods of investigation and prediction of outcome is being increasingly recognised as a safe and quicker option, but these can be cost-intensive. Treatment has been challenged with endoscopic third ventriculostomy, although the effectiveness of this treatment is less known in iNPH. Large numbers and longer follow-ups are necessary to answer some of the difficult issues surrounding this condition, but old age and co-morbidity will always limit this.

6.8 Concluding comments

Several guidelines have been derived from the literature in the last decade from different parts of the world. Although there is little variation in their recommendation we are in a better position to manage these patients from the information available. Although this study was not able to identify those who will respond to a shunt from their age, etiology, duration of symptoms and classical triad, it supports the literature that a typical clinical presentation and radiological diagnosis along with CSF hydrodynamic testing, including an ELD for improvement was able to produce a 73% good response to shunt at 1 year. An Rcsf of >12 mmHg/ml/min can be recommended as a cut off above which good surgical outcomes may be seen but this cannot be used on its own. The initial and late risk of shunting can be avoided by using a programmable shunt and performing an early scan a few weeks after surgery and a later scan to identify late subdural collections. The early complications of subdural collections can be avoided by setting the pressure between 110 and 130 mmH2O and gradually reducing over time. Overall a systematic approach to investigate these patients based on a protocol can identify shunt responsive patients with higher success rates, but we haven't identified any non-invasive tests

that will predict those who will benefit a shunt. The long term follow up of these patients is necessary to account for further clarification of this protocol. It is proposed to continue this work in its entirety along with some modifications and further non-invasive investigations in the future and collaborate to set up a multicenter study in the United Kingdom.

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Appendix

Appendix 1: Patient and Relative information leaflet

Royal Preston Hospital
Lancashire Teaching Hospital NHS Trust
Department of Neurological Surgery
Sharogreen Lane, Fulwood, Preston PR2 9HT

Research Project: Normal Pressure Hydrocephalus - Identifying the most appropriate investigation in shunt responders.

Welcome to the Royal Preston Hospital. You have been admitted to the hospital for evaluation of a condition called **Normal Pressure Hydrocephalus (NPH),** which you may be suffering from. It is characterised primarily by gait (walking) problems, dementia (memory problems), and urinary incontinence. You are invited to take part in a study as part of identifying the most appropriate investigation and measuring outcome following treatment in this group of patients. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your family and doctors to clarify any queries.

What is Hydrocephalus?

Hydrocephalus is an abnormal (excessive) accumulation of cerebrospinal fluid, commonly referred to as CSF in the head. The CSF is located and produced within cavities of the brain called ventricles**.** The function of CSF is to cushion the delicate brain and spinal cord tissue from injuries and maintain proper balance of nutrients around the central nervous system. Every day your body produces a certain amount of CSF and that same amount of CSF is absorbed in the brain. When an imbalance occurs, an excess of CSF fluid builds and if left untreated, will create increased pressure in the head and may result in increased symptoms or brain damage.

What is Normal Pressure Hydrocephalus?

Normal pressure hydrocephalus (NPH**)** is a type of hydrocephalus, which normally occur, in older adults. NPH is an accumulation of CSF, which causes the ventricles of the brain to enlarge. The enlarged ventricles of an NPH patient may not cause increased intracranial pressure, as is the case with most types of hydrocephalus. The abnormal accumulation of CSF, causing enlarged ventricles, is thought to stretch the nerve tissue of the brain causing a various symptoms. NPH normally occurs in adults 60-years and older, and in as many as 10% of all patients with symptoms of dementia. Some patients with some of the same symptoms as dementia, Alzheimer's, or Parkinson's may actually have NPH. Unfortunately, NPH can be difficult to diagnose and many times goes untreated.

What causes it?

For most patients the cause of NPH cannot be determined. In some cases, history of previous brain injury or surgery can result in hydrocephalus. In other cases, the imbalance in the production or absorption of CSF causes the hydrocephalus. Diagnosis of NPH is often difficult due to the symptoms being similar to other disorders like mild dementia, Alzheimer's, Parkinson's or simply old age factors.

What are the symptoms of NPH?

Characterized by three primary symptoms, a triad of gait disturbance (difficulty in walking), dementia, and urinary incontinence**. Gait disturbances** range in severity, from mild imbalance to the inability to stand or walk at all. The gait is wide-based, short, slow and shuffling and may have trouble picking up their feet, making stairs and kerbs

difficult and frequently resulting in falls. **Mild dementia** can be described as a loss of interest in daily activities, forgetfulness, difficulty dealing with routine tasks and short-term memory loss. People do not usually loose language skills, but they may deny that there are any problems. **Impairment in bladder control** is usually characterized by urinary frequency and urgency in mild cases, whereas a complete loss of bladder control (urinary incontinence) can occur in more severe cases. However, not all symptoms are always apparent. Because these three symptoms are often associated with the aging process in general, and a majority of the NPH population is older than 60 years, people often assume that they must live with the problems or adapt to the changes occurring within their bodies. Symptoms can be present for months or even years before a person sees a doctor. The symptoms of NPH seem to progress with time and the rate of progress is variable. As a general rule, the earlier the diagnosis, the better the chance for successful treatment, but some people experiencing symptoms for years can improve with treatment.

How is it diagnosed?

Once the diagnosis of NPH is suspected there is no single perfect test to determine if a patient will respond to treatment. The most common diagnostic tools are doing a scan of the head CT or MRI, which you may have already had. To make a more precise diagnosis one or more of these tests may have to be performed which include Magnetic resonance imaging (MRI), lumbar puncture, measurement of cerebrospinal fluid outflow resistance, continuous lumbar CSF drainage, walking tests and neuropsychological testing. Please find attached on a separate piece of paper, details of each investigation.

What is the treatment for NPH?

The treatment of choice for NPH patients who show a positive response to diagnostic testing is the placement of a VP (ventricular peritoneal) shunt. A shunt is an implantable device designed to drain CSF which has two components: a catheter, the tubing that transports and diverts the CSF from the ventricles to the abdominal cavity where it is easily absorbed, and a one-way valve that regulates the pressure or flow of CSF away from the ventricles of the brain, thereby allowing the enlarged ventricles to return to a normal state. This requires a surgery under general anaesthesia the details will be explained including the risks when a decision is made. This technique is very effective in improving the troubling symptoms of NPH. There are two types of shunts a traditional fixed pressure valve shunt or a pressure programmable shunt. The choice depends on each individual case. You will generally need to stay in the hospital on an average between three to seven days following an operation.

Will this treatment work?

If the cause of NPH is known, success rates can be as high as 80 percent. In cases in which a cause is not known, the success rate varies from 25 to 74 percent. The higher success rates, however, have been reported from centres using the more demanding diagnostic tests, as you will undergo in our study. Your symptoms may improve within days of shunt surgery which ranges from mild to dramatic, or may take weeks to months to abate. However, there is no way to predict how fast, or to what extent, this improvement will occur. It is also not possible to make general predictions of how long the improvement will last, as the course of clinical improvement varies for each patient. Unfortunately, there are no guarantees.

Are there any restrictions to life after the surgery?

Generally, there are no restrictions to daily activities, except those involving great physical exertion. We will discuss with you any restrictions that may be needed. Most patients with hydrocephalus can look forward to a normal future. Shunts are expected to perform reliably over a long period of time. Follow-up visits will be necessary to check post-operative status and resolution of symptoms.

Do I have to undergo these tests and who will do them?

You are only suspected to have this condition and in order for us to diagnose and decide the appropriate treatment you will have to undergo the tests mentioned. The tests are simple and straightforward but carry very small risks, which will be, explained. The tests will be carried out in a systematic manner by one of the doctors. You will also meet a physiotherapist and nurse who may also perform some tests.

Will my family be involved in the decision-making?

Yes, feedback from family and friends especially during the period of investigation will guide us in decision-making. They can take part in the various discussions and feel free to ask any questions on your behalf.

Conclusion:

These are some of the facts about normal pressure hydrocephalous. If you did not understand any of the information feel free to ask any questions to Mr.G.Balamurali, one of the doctor, who will be responsible for conducting your investigations. The consultant looking after you will make the final decision.

Investigations for Normal Pressure Hydrocephalus

A brief description of the various tests, and their significance, which you will be undergoing has been explained. Various personnel's including a radiographer, physiotherapist, nurse and a doctor will perform these tests. Tests may be repeated. Please do ask us if you do not understand.

MRI flow scan:
Is safe and painless, and will take approximately 30 minutes or longer. MRI uses radio signals and a very powerful magnet to create a picture of the brain. It will be possible to detect if the ventricles are enlarged as well as evaluate how fast CSF moves through a particular part of the brain called the cerebral aqueduct, which may provide information about the surrounding brain tissues. Patients with cardiac pacemakers or certain other metallic implants cannot have MRI scans because of potential interference with the pacemaker. This machine can be claustrophobic and you will need to lie down still for about 30 minutes.

Walking tests:
You will be asked to walk a fixed distance usually 10 metreeters. Your pattern of walking, speed and time will be noted. This test will be repeated after a spinal tap to look for any improvement.

Neuropsychological Tests and CANTAB:
This testing involves asking a series of questions used to determine if there is a loss of brain function due to hydrocephalus. You will also undergo some tests on a touch screen computer. Tests will be repeated after a lumbar puncture.

Lumbar Puncture or spinal tap:
This allows an estimation of CSF pressure and analysis of the fluid. Under local anesthetic, a thin needle is passed into the spinal fluid space of the low back. This test may be slightly uncomfortable but is a very valuable diagnostic tool. Following a spinal tap CSF outflow and drainage tests can be performed.

Measuring CSF outflow resistance:
This is a more sophisticated test done during a spinal tap. It requires the simultaneous infusion of artificial spinal fluid and measurement of CSF pressure. In essence, this test assesses the degree of blockage to CSF absorption back into the bloodstream. If the calculated resistance value is abnormally high, then there is a very good chance that the patient will improve with shunt surgery.

Lumbar catheter insertion:
This is a variation of the lumbar puncture or usually done after a spinal tap, a thin, flexible tube (catheter) is passed into the spinal fluid and the needle is removed. The lumbar catheter allows continuous removal of spinal fluid over two days imitating the effect that a shunt would have. You will not feel any pain but will feel its presence. It will be removed after two days and some of the tests repeated. Patients who respond dramatically to such spinal fluid drainage are likely to respond to shunt surgery.

Appendix 2: Consent form

Royal Preston Hospital.
Lancashire Teaching Hospital NHS Trust
Department of Neurological Surgery

Title of Project: Normal Pressure Hydrocephalous - Identifying the most appropriate investigation in shunt responsive patients.

Name of Researcher: Mr G Balamurali

Please initial box

1. I confirm that I have read and understand the information Sheet dated ……. (NPH03 version 2) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

Name of patient	Date	Signature
Name of Next of Kin/Carer *(If patient not competent to give consent)*	Date	Signature
Name of researcher	Date	Signature

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes.

Appendix 3: National Adult reading Test

(Abbreviated version)
Hazel E. Nelson

Please read aloud the following words

CHORD	**NAIVE**
ACHE	**CATACOMB**
DEPOT	**GAOLED**
AISLE	**THYME**
BOUQUET	**HEIR**
PSALM	**RADIX**
CAPON	**ASSIGNATE**
DENY	**HIATUS**
NAUSEA	**SUBTLE**
DEBT	**PROCREATE**
COURTEOUS	**GIST**
RAREFY	**GOUGE**
EQUIVOCAL	

Appendix 4: Beck Depression Inventory

Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Do not choose more than one statement for any group.

Appendix 5: Mini Mental scoring Test (MMSE)

1. Orientation **Scores**

Year	Month	Day	Date	Season	(1-5)
Country	County	Town	Hospital	Ward	(1-5)

2. **Registration**

Name three objects	(0-1)
Repeat	(0-1)
Repeat three times	(0-1)

3. **Attention**

Serial numbers 7s :100,93,86,79 or	(1-5)
Word backwards: CARPET=t,e,p,r,a,c…	

4. **Recall**

Recall the three objects	(1-3)

5. **Language**

Name objects shown by examiner: pencil, tie, watch…	(1-2)
Repeat (No *if ands, buts*…)	(0-1)
3-Stage command *(take this piece of paper in your right hand, fold it in half and place it in the chair next to you)*	(1-3)
Obey written command	(0-1)
Write a senence	(0-1)

Copying (*Copy the figure below)* (0-1)

Appendix 6: Instruction to patient

Appendix 6.1: Instruction for Verbal fluency FAS test

"I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say "B" you might want to give me "bad, battle, bed….."etc. I do not want you to use words which are proper names such as "Blackpool, Bob or Brylcream". Also do not use the same word again with a different ending such as "eat" and "eating". Any questions please? Begin when I say the letter. The first letter is F. You may go ahead. Now begin timing. The three letters F, A and S are given continuously one after the other.

Appendix 6.2: Instruction for verbal fluency – Animal test

"I am going to tell you the names of some things you can find in the kitchen: spoons, knives, forks, plates etc. Can you think of other things in the kitchen?" Allow the patient to name a few things and correct if they produce incorrect responses, explaining the task again. Then say: "now tell me the names of as many animals as you can." Allow 1 minute. If the patient discontinues before the end, encourage them to produce more names. Repeat the basic instructions and give a starting word like "dog" if there's a pause of 15 seconds or more. Allow extra time if you gave them repeat instructions.

Appendix 6.3: Clock drawing test

"I want you to draw the face of a clock with all the numbers on it. Make it large." After completion of the clock face, instruct as follows: "Now, draw the hands pointing at 20 to 4".Instructions may be repeated or rephrased if the patient does not understand, but no other help should be given. The time taken to complete the task may be noted although this has not been used in this study.

Appendix 6.4: 10 metre walking test

The instruction given to the patients for the walking test was, “You see that chair over there, please walk towards it, at your usual speed. Please start walking when you are ready”. Total number of steps and time taken to walk a distance of 10 metres was noted.

Appendix 7: Copy of Ethical Approval