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SAKARI SAVOLAINEN

Diagnosis, treatment and outcome of treatment of normal pressure hydrocephalus

Neurosurgical follow-up study of 5 years

Doctoral dissertation

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Series editors:
Professor Esko Alhava, M.D., Ph.D.
Department of Surgery

Professor Martti Hakumäki, M.D., Ph.D.
Department of Physiology

Author's address:
Department of Neurosurgery
Kuopio University Hospital
P.O.Box 1777
FIN-70211 KUOPIO
FINLAND
Tel. +358 17 172 317
Fax +358 17 173 916
E-mail: sakari.savolainen@kuh.fi

Supervisors:
Professor Matti Vapalahti, M.D.
Department of Neurosurgery
University of Kuopio

Keijo Koivisto, M.D.
Department of Neurology
University of Kuopio

Reviewers:
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ABSTRACT

A total of 314 patients with symptoms of normal pressure hydrocephalus were investigated during the years 1993-2001. Of those patients, 51 were examined following a prospective study protocol. Patients were followed up clinically for 5 years. The non-invasive tests were repeated 3 months and 1 year post-operatively.

The leading symptoms were memory difficulties (84%), walking disability (80%) and urinary incontinence (49%). The study population consisted of 27 male and -24 female patients and the mean age was 66.5 years. Twenty-five of the patients had increased ICP, and these were shunted.

Immunohistochemical studies indicated AD or a high risk to develop AD in 37% of the patients, whereas other neuropathological studies showed change a in 33%.

Only one neuropsychological test, recognition of words, showed significant difference between patients who needed a of shunt and who did not.

Auditory evoked potentials showed shortened latencies and increased amplitudes in patients with concomitant AD compared with those with only NPH. The differences were significant.

MRI studies showed smaller hippocampi in patients with confirmed AD compared with patients with proven or with symptoms indicating NPH. MRI was not able to differentiate patients with NPH from the rest of the study group.

During the 5-year postoperative follow-up 8 patients out of the 25 with increased ICP and 9 patients from the remaining 26 patients died. None of the deaths were shunt related. Of all symptoms walking disability improved most after shunting. The improvement in quality of daily living still remained 5 years after shunting in 47% of patients. Surgery did not improve the patient's rating in any single neuropsychological test.

National Library of Medicine Classification: WL 350, WL 368

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to Anniina and Päivi

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Kuopio, June 2002

Sakari Savolainen

ABBREVIATIONS

AD	Alzheimer's disease
AERP	Auditory event-related potentials
βA4	β-amyloid
BS	Bielshowsky silver
CMCT	Central motor conduction time
Cout	Conductance to outflow
CSF	Cerebro spinal fluid
CT	Computed tomography
EEG	Electroencephalogram
ERP	Event related potentials
GD	Gait disturbances
HDSIN	Size of left hippocampus
HDX	Size of right hippocampus
HE	Hematoxylin and eosin
HV	Healthy volunteers
ICP	Intracranial pressure
MMN	Mismatch negativity
MMSE	Mini mental status examination
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangels
NP	Neuritic plaques
NPH	Normal pressure hydrocephalus
NPHall	NPH patients
NPHAD+	NPH patients with cortical AD pathology
NPHAD-	NPH patients with no cortical AD pathology
n.s.	not significant
PHF-τ	Paired helical filament-tau
Pts	Patients
Rout	Resistance to outflow
S.D	Standard deviation
UI	Urinary incontinence

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to by Roman numerals:

I Prevalence of Alzheimer's disease in patients investigated for presumed normal pressure hydrocephalus: a clinical and neuropathological study. S.Savolainen, L.Paljärvi and M, Vapalahti, Acta Neurochir (Wien);141:849-853, 1999

II MRI imaging of the hippocampus in normal pressure hydrocephalus: correlations with cortical Alzheimer's disease confirmed by pathologic analysis. Sakari Savolainen, Mikko P Laakso, Leo Paljärvi, Irina Alafuzoff, Heleena Hurskainen, Kaarina Partanen, Hilkka Soininen and Matti Vapalahti, Am J Neuroradiol;21: 409-414, 2000

III Auditory event-related potentials differentiate patients with normal pressure hydrocephalus and patients with concomitant Alzheimer's disease verified by brain biopsy, Sakari Savolainen, Jari Karhu, Ari Pääkkönen, Leo Paljärvi, Juhani Partanen, Irina Alafuzoff and Matti Vapalahti, Neuroreport 12(1);33-37, 2001

IV Five-year outcome of normal pressure hydrocephalus with or without a shunt: Predicitive value of the clinical signs, neuropsychological evaluation and infusion test. S.Savolainen, H. Hurskainen, L.Paljärvi, I. Alafuzoff and M.Vapalahti. Acta Neurochir (Wien), 2002 (in press)

V Brain biopsy prior to treatment of Alzheimer's disease. Anna Holm, Sakari Savolainen and Irina Alafuzoff. Minimally Invasive Neurosurgery, 2002 (in press)

CONTENTS

Introduction

Hydrocephalus refers to an increased volume of cerebrospinal fluid (CSF) within the head without a definition of its location.

Obstructive or non-communicating hydrocephalus occurs when a lesion or stricture impedes free passage of the CSF from the lateral ventricles to the subarachnoid space (1). Communicating hydrocephalus refers to the abnormality in which there is free passage of CSF from within the ventricular system in the subarachnoid space but there is still failure of CSF absorption with dilatation of the lateral ventricles and the third and fourth ventricles (1).

The clinical picture of hydrocephalus in its classical form is well known: a decrease in the level of consciousness, headache and vomiting. On the other hand, if it is not clear, the diagnosis of hydrocephalus can be missed when the increase in intracranial pressure is marginal and symptoms of raised pressure are lacking. The clinical picture may then be obscure and may mimic totally different diseases.

In normal -or 'low'-pressure hydrocephalus (NPH), intracranial pressure is not continuously pathological and the symptoms may develop very slowly. The syndrome is sometimes called Hakim-Adam's syndrome after the researchers who first described this entity (1, 76).

Since the times of Hakim's original publication 1965 (76), the number of reports on the subject have increased steadily. The main symptoms of NPH include gait difficulties, progressing memory loss and urinary incontinence.

Several investigators have described different methoda to reveal the syndrome behind the symptoms of NPH (18, 22, 29, 36-38, 40, 54, 73, 75, 79, 82, 92, 98, 100, 141, 146, 148, 152-154, 172). Most of the methods used for

diagnosing NPH deal with ICP changes and CSF dynamics (1, 18, 22, 23, 27, 33, 60, 61, 75, 84, 92, 98, 104, 111, 114, 118, 123, 164, 173). The treatment of normal pressure hydrocephalus was first based on the clinical picture of the disease and only about 25% of patients benefited from surgery (5).

Shunt treatment for patients with increased ICP result in improvement in 40-60% of cases (13, 82, 85, 108, 171). Many patients do not respond to shunt surgery. The reason for this is often not found, and for them curative treatment is not easy to find for these patients.

Elderly patients with dementia and gait disturbances may have Alzheimer's disease, as it is the most common non-vascular dementia. This may happen even when all diagnostic criteria of NPH are fulfilled. Patients having NPH ought to be identified earky because pressure waves may produce irreversible changes, and when treated early enough these patients may recover completely even from a wheel-chair state.

REVIEW OF THE LITERATURE

1.History of diagnosis of normal pressure hydrocephalus

Patients having symptoms of normal pressure hydrocephalus were described during the first half of the 20th century (50). More detailed descriptions were published in 1965 by Adams and Hakim (1, 76). These publications pointed out that patients with enlarged ventricles and walking disability can be treated with a shunt despite a normal lumbar CSF pressure. They observed that their patients had a triad of symptoms, which since then have been considered typical for this entity. However, less favourable outcomes from shunting have been reported in patients having similar symptoms and treated with a shunt (4, 170). A discrepancy between radiological diagnosis and clinical picture has been pointed out for cases with less favourable outcome (84) Not all the patients with enlarged ventricles do suffer from NPH. The non-responders may have an other disease, either concomitantly with NPH or alone, e.g cerebrovascular or Alzheimer's disease (131, 172).

Later on the diagnostic accuracy of NPH has improved. New methods have been introduced, but despite all this development, less than 80% of patients with NPH benefit from surgery (81, 85, 107).

2.Epidemiology of normal pressure hydrocephalus

Normal pressure hydrocephalus is a treatable cause of dementia (32, 36, 39, 52, 53, 72, 88) of which the precise epidemiological data are lacking. In some series, NPH accounts for 0 to 6% of cases of dementia (39, 105) and progressive memory loss. In Freter and co-workers' epidemiological study only 4 out of 196 (2%) patients had NPH as the cause of dementia (52).

Alzheimer's disease (AD) is the major cause of age related dementia, possibly accounting for as much as 80% of the total demented population (96, 98, 162, 167, 175). Of all people older than 65 years 11.2% are afflicted with AD (44, 87, 162, 167). This means that there are about 40-50 000 patients with AD in Finland. Prevalence of NPH is not known, incidence in this series was 317 patients in 7 years/ 1000 000 people, which means about 5 patients/100 000/year.

3.Clinical picture of normal pressure hydrocephalus

The clinical picture of NPH is a triad of symptoms, which includes gait disturbances (GD), urinary incontinence (UI) and memory loss. The triad is seldom complete in patients with NPH, and the proportion of different classical symptoms varies a lot. Walking disability, as a symptom of NPH, is reported to be present in 11-95% of cases, while 24%-96% have mental disturbances, and urinary incontinence is seen in 45-90% of cases. Only 56% of patients have the complete triad (13, 35, 45, 48, 69, 74, 82, 107, 130, 138, 171). The absence of GD or onset of GD after the beginning of dementia predicts poor outcome (14, 69, 70). The presence of the full triad has been described as a favourable sign for positive outcome after surgery (40).

3.1 Cognitive functions

Dementia is an acquired syndrome of intellectual impairment due to brain dysfunction. It can be caused by various kinds of diseases. It manifests as loss of memory and orientation, and finally people can not eat, may become bedridden and the disease may lead to death.

Patients with NPH have a slight or moderate degree of memory loss. The mental deficit resembles frontal disorders, the most prominent features being forgetfulness, inertia, inattention, and a decreased ability to perform complex tasks, and to make use of acquired information (71, 88, 139, 147, 150, 168). It has been suggested that when dementia predominates in the clinical picture, concomitant AD should be suspected (65). Dementia as first presenting symptom is considered a negative prognostic factor in the outcome of NPH (10, 67, 69), as is long duration of dementia before shunting (69, 70). Of NPH symptoms, dementia is least likely to improve after a shunt operation (147).

However, AD is the most common and best known of dementing processes (167). Less frequent forms of dementia are

due to extrapyramidal symptoms like Parkinson's disease and Lewy body -dementia (89).

3.2.Walking disability

Gait difficulty is usually the first symptom, often the only apparent clinical sign, and after shunting it often improves better than the other NPH symptoms. Gait symptoms include difficulties in initiating walking, postural instability and a short- stepped shuffling gait (45, 69, 85, 138). The patients walk typically with wide basis and short steps. The feet seem to be stuck to the floor. The term 'gait apraxia' has been commonly used. Sometimes walking can mimic the gait of Parkinson's disease (124, 159). Gait difficulties may be due to stretching or destruction of the paraventricular corticospinal fibers, disconnection of basal ganglia from the frontal cortex, uninhibited antigravity reflexes, and cocontraction of agonists and antagonists during walking. Vascular ischemia due to compression of vessels caused by enlarged ventricles may be present (45).

3.3 Urinary incontinence

Urinary incontinence is a late sign (124). An increased urgency is almost always present but sometimes patients tend to ignore their incontinence. Consequently, ignorance specific inquiries are required to elicit information on this symptom (47). Incontinence as the only symptom was described by Fisher 1982 (47). Urinary incontinence is due to impairment of supraspinal control caused by damaged periventricular pathways to the sacral bladder centre, with subsequent decrease in inhibition of bladder contractions.

3.4 Other symptoms

Apart from the conventional clinical triad, other symptoms of NPH have also been reported. Motor disturbances other than walking disability, such as the problems with equilibrium, have been reported (15). Sometimes patients with NPH have psychiatric disorders i.e. paranoia and obsessive-compulsive type of behaviour (16, 133, 143). These symptoms are far less common than those of the classical triad are.

4.Pathophysiological considerations

Patients with normal pressure hydrocephalus have enlarged ventricles and only moderately raised ICP. Normally, cerebrospinal fluid (CSF) is produced at a rate of 20ml/h and the production and resorption are in balance. In hydrocephalus there is either increased production or decreased resorption of cerebrospinal fluid CSF (111). In NPH, CSF production has been found to be unchanged or even reduced by up to 50% (23, 61, 111).

Subarachnoid haemorrhage is considered the cause in about one third of all cases of normal pressure hydrocephalus (50, 92, 124). Other causes, such as head trauma, meningitis, craniotomy, cerebral tumours and any other diseases affecting the central nervous system represent about one third of cases. Idiopathic NPH, i.e. for which thorough investigations do not reveal the aetiology, accounts for one third of cases. In such cases the cerebral blood flow may be decreased resulting in ischaemia in the deep white matter (31). Other vascular conditions, for instance venous compromise, can be a cause of NPH (6, 26, 28, 30, 137). Other etiological factors have been presented and the cause of NPH is thought to be multifactorial (131). Bech and co-workers reported that there was no correlation between an increased ICP and biopsy findings from the leptomeninx and brain (7).

Table 1 Aetiology of normal pressure hydrocephalus

-Subrachnoid haemorrhage	1/3
-Other central nervous system diseases	1/3
-Unknown	1/3

5. Diagnostic investigations in NPH

5.1 Clinical assessment

Thorough clinical examination is essential in patients with NPH. Typically, patients have suffling gait, urinary incontinence and progressive memory loss. It is difficult to base diagnosis only on clinical findings alone, as for instance gait disturbance resembles aspecific senile gait disorder with pyramidal and cerebellar signs (10). In Vanneste's report, the rate of improvement in patients with clinically and CT-based diagnosis of NPH was only 29% (171).

5.2 Computerised tomography

Computerised tomography has been the simplest and most frequently used tool in diagnosing NPH. The findings are ventricular enlargement, especially in the temporal horns (84, 177), widening of the third ventricle, periventricular hypodensity, and flattening of cortical sulci (23). Wikkelsö and co-workers noticed that in those patients who improved after surgery the temporal horns were wider than in non-responders. On the other hand, no single feature in CT - scanning could distinguish responders from non-responders (171, 177). Kitagaki and co-workers reported that enlarged basal cisterns and sylvian fissures and focally dilated sulci support the diagnosis of NPH (95). Other dementing diseases may, however, have the same features on CT scans (41). Temporal lobe atrophy is a characteristic feature in Alzheimer's disease (57). The Evan's index is the ratio between the maximum width of the frontal horns and the maximum width of the inner table of the cranium (46), and it is used to determine the pathological growth of ventricles. It enabled the development to be followed on a series of CT scans. However, a favourable change in the Evan's index did not

correlate with clinical improvement after shunt surgery (22, 108, 168).

5.3 Magnetic resonance imaging

In magnetic resonance imaging (MRI) the basic diagnostic findings in the brain are similar to those in CT (large ventricles, flattened sulci and periventricular hypodensity) (27-29, 48, 62). The size of the ventricles has been shown to increase with age and to correlate with worsening of memory (163). To improve the diagnostic accuracy of NPH, a method to estimate the size of ventricles has been introduced (179). To improve NPH diagnostics among patients with large ventricles, a method similar to Evan's ratio but based on the ventricular/intracranial volume ratio has been developed. A high ratio is believed to correlate with NPH. One advantage of MRI over CT is its ability to produce sagittal and coronal planes. Differential diagnosis of NPH such as deep white matter infarctions and multi-infarct dementia can better be found with MRI (28, 31, 86, 166).

With MRI, the movements of CSF in cerebral CSf pathways can be measured either with absolute values or from the so-called flow void sign, which means loss of signal because of increased CSF flow in the aqueduct (5, 30, 91, 119). In normal elderly people the aqueductal stroke volume is about 10-20 mm3/sec. In patients with hydrocephalus the stroke volume has been elevated up to 50mm3/sec. Bradley and co-workers reported hyperdynamic CSF flow in communicating hydrocephalus, and claimed that this was particularly true for those who responded well to shunting (30). But, Krauss and co-workers, in their series of 37 patients with idiopathic NPH, did not find any correlation between flow-void and favourable outcome from a shunt (101). On the other hand, Hakim and co-workers reported that the predicting value of MRI- detected CSF flow was higher than that of a lumboventricular infusion test.

Efforts have been made to differentiate patients with NPH from those with Alzheimer-type dementia by measuring the volumes of hippocampus (63) (65) and perihippocampal fissures (83). This method has been of some prognostic value to the effect of shunt surgery (64). Alzheimer's disease can be differentiated from Parkinson's disease and vascular dementia with this method (78, 102, 103).

5.4 Intracranial pressure measurement and hydrodynamic tests

Intracranial pressure monitoring is widely accepted as the diagnostic method of choice in NPH (140, 141, 148, 152), and in assessing the need of a shunt in patients with symptoms of NPH (141). The pressure may also be recorded intrathecally (144).

So- called A -waves have been reported to last up to 30 minutes with amplitudes up to 100mm Hg. Such waves can also be seen in NPH, but with much lower amplitudes (141). B waves with frequencies between 0.5 and 2/min can be found in normal subjects (120).The occurrence of B -waves is reported as a percentage of the total recording time. There are different interpretations of where to draw the line of abnormality, and percentage -values between 5 and 50 from total recording time have been suggested. (139). In patients who are likely to respond to shunt surgery the intracranial mean pressure is above 9mm Hg-15mm Hg (70, 139, 147).

Different opinions of the usefulness regarding ICP recording have also been expressed. It is not available in all neurosurgical centers and it requires good equipment and experienced staff, it is invasive, and no specific pressure findings can be regarded as diagnostic (33). The main disadvantage of prolonged intraventricular ICP recording is obviously the risk of infection, which is about 4% (165). However, the risks of ICP recording, like any other surgical procedure, are minimised when it is used as a part of routine practice.

Several methods have been introduced to measure outflow resistance of CSF (23, 59, 60, 92). Katzman introduced a constant infusion method for measurement of CSF absorption (92) in which they infused artificial CSF via a lumbar needle intrathecally with constant infusion speed and measured the pressure through the same needle. Many studies and different infusion tests have been introduced subsequebtly (59, 164). On the basis on the amount of infused CSF and the rate of infusion the resistance to outflow (Rout) and the conductance to outflow (Cout) of CSF can be calculated using a special mathematical formula.

The predictive value of these studies have varied in different reports (21, 23, 40, 60, 61, 123). The Dutch NPH investigating group (18) reported that Rout ≥12mm Hg/ml/min predicted benefit from shunting, whereas an earlier report claimed the limit value to be 10 mm Hg/ml/min (98). The limit of Cout to show favourable outcome is said to be 0.05-0.12 ml/min/mm Hg (22, 60, 114, 168).

5.5 Temporary CSF drainage

Removal of CSF via lumbar puncture is performed to diagnose NPH by simulating shunt placement (100) and to produce clinical relief of symptoms (155). This method is commonly used in many centers although there ares no controlled research data. Krauss and co-workers reported a 15- to 24- ml removal of CSF, and in Sand and co-workers' study the amount of removed CSF was 40 ml at one time (100) (155).

The advantages of this method are that it is easy to perform rapid, and no specific technical equipment is needed (33). One of the main disadvantages is that false negative results are common. It may be difficult to detect clinical improvement in elderly patients afflicted with headache or other disturbing post puncture symptoms.

CSF tapping has been reported to help to predict outcome after shunting (73, 176, 178). The removal of CSF

affects mainly the gait, but other symptoms may also be relieved (38, 100, 114, 158). In some recent reports it is still suggested to be the most accurate method in evaluating the prognosis after shunt surgery (82). In Malm and co-workers' study the CSF removal could not predict improvements in gait nor in activities of daily living, even though acute improvement in walking after CSF removal was seen (114).

5.6 Cisternography

One of the techniques to detect disturbed CSF circulation is cisternography with intrathecal injection of either gamma-ray emitting radionuclide (isotope cisternography) or non-ionic contrast material, followed by serial computed tomography (CT cisternography). Movement of either material in CSF pathways is followed-up to visualise CSF dynamics (37, 106, 173). In a quantitative cisternography with a radionuclide isotope, a positive correlation between the clearance of isotope and favourable shunt surgery has been reported (106). In Benzel and co worker's study cisternography did not provide additional information (10).

5.7.Neurophysiological studies

Quantitative EEG can not differentiate patients with dementia frpm those with NPH (154). EEG slowing has some correlation with the outflow resistance, but that is not of clinical value in diagnosing NPH (154).

It has been noticed that there is a significant difference in the motor- evoked potentials measured preoperatively between responders and non-responders after shunt surgery (180). On the other hand, Zaaroor and co-workers did not find any difference in latencies between preoperative and postoperative measurements in central motor conduction time (CMCT). Moreover, patients who responded to surgery had

normal CMCTs preoperatively, whereas those with delayed preoperative CMCTs did not benefit from surgery.

Event- related potentials (ERPs) (142) have been reported to differentiate normal healthy subjects from demented ones (66). A recent study (146) suggested that event-related potential recordings together with other neurophysiological studies predict a favourable outcome after surgical procedure in patients with raised intracranial pressure. However, conflicting results have been reported (79). No single specific predictive test or test pattern is yet available for the preoperative evaluation of the cognitive state in NPH, although auditory discrimination may be impaired, for instance in Parkinson's disease.

5.8. Neuropsychological tests

Different well- validated tests have been introduced to find neuropsychological deficits in various neurological problems (3, 24, 34, 49, 68, 110, 125, 126, 145, 149, 160, 174, 175). These tests are very thorough and thus time-consuming. Education seems to affect test results (96). A practical bed-side tool to test cognitive functions is the Mini Mental Status Examination (MMSE-test) (49, 68). If the score of this test is low i.e. under 24 out of a maximum 30 possible (88), dementia is probably due to other causes than NPH.

Neuropsychological testing is an element in only a few reports regarding evaluation and follow-up of patients with hydrocephalus. Gustafsson and Hagberg (72) noticed that careful psychometric tests are necessary to diagnose hydrocephalic dementia. One report says that if preoperative cognitive impairment was severe, the chances of postoperative recovery were poor (88). The varying results given by neuropsychological testing indicates the heterogeneity of NPH -syndrome (88). Patients with suspected NPH seem to have

poorer surgical prognosis if they have language deficits preoperatively (68).

6.Differential diagnosis of NPH

It is important to differentiate other dementias when diagnosing NPH. Alzheimer's disease (AD) is the major cause of age-related dementia and it has a central position in the differential diagnosis of NPH (58). Deteriorating memory and other cognitive functions are the most profound symptoms in AD. Gait disturbances and urinary incontinence are also seen in patients with AD (134, 161). The diagnosis of AD is often clinically supported by neuroradiological and neuropsychological tests without the need of invasive techniques. In practice, diagnosis is based on typical features of the disease and exclusion of other conditions which might be responsible for dementia (121).

However, the diagnosis at the very onset of AD is thwarted by the heterogeneity of the symptoms. Earlier studies estimate the accuracy of the clinical diagnosis to be about 80% compared with post mortem confirmation (17, 51, 55, 56, 127, 128). The diagnosis can accurately be determined only with neuropathology, but methods, such as brain biopsy to improve the premortem diagnosis are rearly used (9, 11, 25, 42, 80, 93, 94, 115-117, 127). Neurofibrillary tangels (NFT), which are diagnostic in AD, are sometimes present in the brain of patients with NPH (43).

The diagnosis can be facilitated by neuroimaging techniques. In particular, magnetic resonance imaging (MRI) studies with hippocampal volumetry to evaluate hippocampal atrophy has been shown to differentiate patients with early AD from control subjects with 85 - 95 % accuracy (90, 102, 103). With volumetry of the hippocampus, AD patients can be distinguished not only from cognitively normal controls, but also from subjects that suffer from benign memory impairment, caused by age-associated memory impairment and depressive pseudo-dementia (90, 102, 103, 109).

Parkinson's disease must be taken into consideration, as the gait disturbance can be very much similar in both

conditions, but there is no spasticity and rigidity in patients with NPH. The therapeutic effect of medication in Parkinson's disease often confirms the diagnosis. Of course, a patient can have both Parkinson's disease and NPH simultaneously. In that case the Parkinson's disease should be first treated with drug therapy, and if NPH is diagnosed, the patient should undergo a shunt operation.

Spinal stenosis effects walking, but the typical clinical picture - back pain with claudication - almost always helps in the selection of adequate investigations. Gait may deteriorate in normal healthy elderly people without any other neurological disease.

7. Treatment of NPH

7.1. Drug therapy

Aimard and co-workers have studied drug treatment in NPH. Acetazolamide has been used to reduce the production of CSF with some success (2). However, there are no controlled studies on the effect of acetatzolamide on CSF production.

7.2.Operative treatment

NPH is usually treated with CSF diversion. The purpose of the shunt is to cut the abnormally high ICP waves and to preserve a normal pressure inside the cranium. Shunting may not only have an effect on clinical symptoms but it may also prevent deep white matter lesions in the brain (99).

Several CSF diversion techniques have been introduced. Ventriculo-atrial and ventriculo-peritoneal shunts are the most common techniques in which the lateral ventricles are connected either to the right atrium or to the peritoneal cavity via a catheter and valve (122, 138). Manufacturers have introduced various kinds of shunt valves. When a differential pressure valve was compared with a variable resistant valve, there was no difference in preoperative and postoperative resting CSF pressure (113). In two studies, valves with different opening pressures were compared (19) and patients treated with shunts with a low opening pressure (40±10 cm H2O) managed better than those treated with valves with a medium opening pressure (100±10 cm H2O) (19, 122). In these series the rate of subdural effusions was lower with patients treated with the medium-pressure valves than (34%) in patients treated with the low-pressure valves (71%). There were no clinical symptoms related to those complications. In Weiner's study there was no difference in outcome or in complication rate

between flow-regulated and differential pressure valves (175). The experience of the surgeon is one of the major factors in avoiding shunt complications (112).

Another operative treatment is third ventriculostomy, in which the floor of the third ventricle is opened. This procedure is best performed with endoscopy but has not been often used in NPH because it does not treat the basic mechanism of NPH, i.e. the deficit of resorption of CSF. Endoscopy can be recommended in cases of aqueductal stenosis, where is a structural change in the brain(124, 129).

8. Outcome and prognosis of NPH after shunt surgery

8.1 Quality of daily living

The clinical efficacy of shunt surgery has been shown to vary between 25% and 80% (1, 13, 70, 76, 108, 157). Cerebral ischaemia is reported to be an important predictor of poor outcome after shunt surgery (20).

In a study by Larsson (107) a success rate of 78% was achieved after careful selection of patients. Eleven per cent of his patients were able to leave long-term care institutions and there was a 36% reduction in the aid required in daily care.

8.2 Cognitive functions

In some reports, neuropsychological symptoms showed considerable improvement after shunt operation (70, 72, 168). In Raftopoulos and co-workers' study an overall recovery rate was seen in 96% of patients, and 66.6% of their patients showed a positive effect in memory functions from shunt surgery after one year (147).

In Tromp and co-workers' report, a spinal tap had no influence on measured cognitive functions. Shunt operations had an effect only on attention after three months' follow-up (169). A visual naming test has been used to predict the possible effect of shunting (70). Patients who passed this test had a better recovery rate than those who failed. The duration of dementia had a predictive value on the response to shunt surgery (70).

A succession rate of as low as 25% was reported in a retrospective analysis of shunt surgery in patients with NPH (170, 171). However, there are studies that support the view that one must not deny patients shunt treatment regardless of the duration of symptoms (107).

8.3 Walking disability

Difficulties in gait are the most likely to improve after shunting (85). In Larsson's series walking improved in 76% of patients (107). Graff-Radford and co-workers reported that gait disturbance prior to dementia may be favourable to the effect of shunt surgery (70). Larsson did not find any symptom predicting good outcome (107). In Raftopoulos' series, walking had improved in as many as 95% of the patients one year after surgery. In the majority of the patients the change took place within two months after surgery (147). The success rates in most series are lower than in these two reports.

8.4 Urinary incontinence

Recovery from urinary incontinence was noticed in 65% of patients after shunt surgery (72). In Raftopoulos' series, there was a 90% success rate in bladder function already 9 days after surgery. The positive effect remained throughout the follow-up (147). In other reports, relief in urinary incontinence after shunting has been reported in 36-76% of cases (99, 114, 138, 175).

AIMS OF THE STUDY

The aims of this study were:

1. To determine the prevalence of Alzheimer's disease in patients with symptoms of normal pressure hydrocephalus. (I,V)

2. To determine the diagnostic value of MRI in distinguishing patients with NPH from patients with AD. (II)

3. To determine the diagnostic value of auditory event related potentials (AERP) in diagnosing AD and NPH. (III)

4. To determine the value of neuropsychological tests in the diagnosing and follow-up of NPH. (IV)

5. To discover the outcome of shunt treatment in NPH patients, and to test the value of clinical signs and infusion test in the prognosis of NPH. (IV)

PATIENTS AND METHODS

1.Patients

Between 1993 and 2001 a total of 317 patients have undergone intracranial pressure recording because of suspected NPH in the Department of Neurosurgery, Kuopio University Hospital. These patients had been referred by neurologists on clinical grounds and CT findings of NPH. There were no patients with suspected NPH who did not undergo ICP recording during that time. The formation of the study population in different substudies is shown in Figure 1.

During the two-year span from November 1993 to November 1995, 51 patients out of those 317, were drafted into a prospective study. The preoperative investigations performed in this prospective series are shown in Figure 2.

The remaining 266 patients were investigated clinically but did not undergo the whole study protocol. Of those 266 patients 162 had both ICP recording and cortical biopsy.

The remaining 104 had only ICP recording.

Immunohistochemical staining was performed from brain biopsies of 213 patients.

Of those 51 patients the prospective study, 17 died during the 5-year follow-up period. The clinical data are available for all 51 patients.

In the MRI study, there were 27 cognitively healthy volunteers and 24 patients with AD outside this study group and fulfilling the clinical criteria for AD. They were used as a reference group.

Figure 1.
The formation of the study population in different substudies.

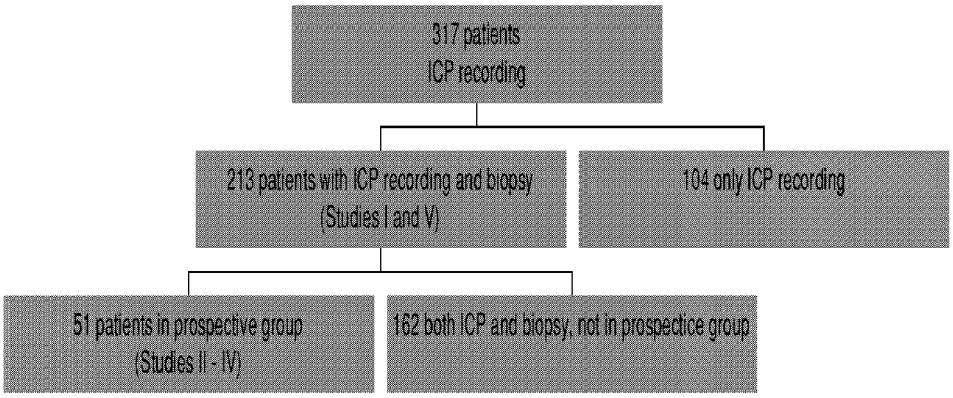
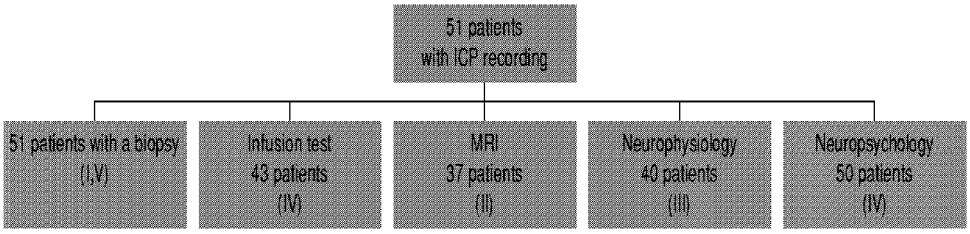


Figure 2.

Preoperative investigations in different substudies.



2.Inclusion and exclusion criteria

The Department of Neurosurgery at Kuopio University Hospital is the only neurosurgical unit in Eastern Finland (with a population about 900 000 inhabitants). Patients with symptoms of normal pressure hydrocephalus are referred to the department for consultation.

The inclusion criteria for the prospective study were:

-age under 75 years

-suspicion of normal pressure hydrocephalus on the grounds of clinical symptoms and CT findings

-informed consent

The exclusion criteria for the study were:

-malignant disease of any kind

-diabetes mellitus over 5 years' duration

-severe coronary heart disease (NYHA 3 or worse)

-anticoagulant therapy

3.1 Study protocol

The protocol included complete clinical examination by the author including MMSE. An MRI -study, a thorough neuropsychological test battery, and neurophysiological tests (evoked potentials and quantitative EEG) were also included in this study. Twenty four-hour intraventricular pressure recording and infusion test were performed, and a cortical brain biopsy was obtained. The non-invasive tests were repeated postoperatively, but MRI was repeated 3 months postoperatively only on those patients who were shunted. In other subjects, CT -scanning was performed.

Patients were followed up for 3 months and 12 months postoperatively at the outpatient department. The final follow-up for all patients was conducted after five years by telephone contact or by a letter.

Table 2. The number of patients in the prospective study protocol at different stages of follow-up

	Before CSF shunt	3 months after shunt	1 year after shunt	5 years after shunt
Clinical data	51	51	50	34
MRI	37	19	0	0
AERP	40	40	38	0
Neuropsychological tests	50	44	38	0

AERP = auditory event related potentials
CSF = cerebrospinal fluid
MRI = Magnetic resonance imaging

3.2 Diagnosis and treatment of NPH

The routine NPH diagnosis in our department on patients with clinical and CT suspicion for NPH is based on intra-ventricular overnight ICP recording and analysis of pressure waves (28) (139) (141) (148) (152). No other investigative procedures were used.

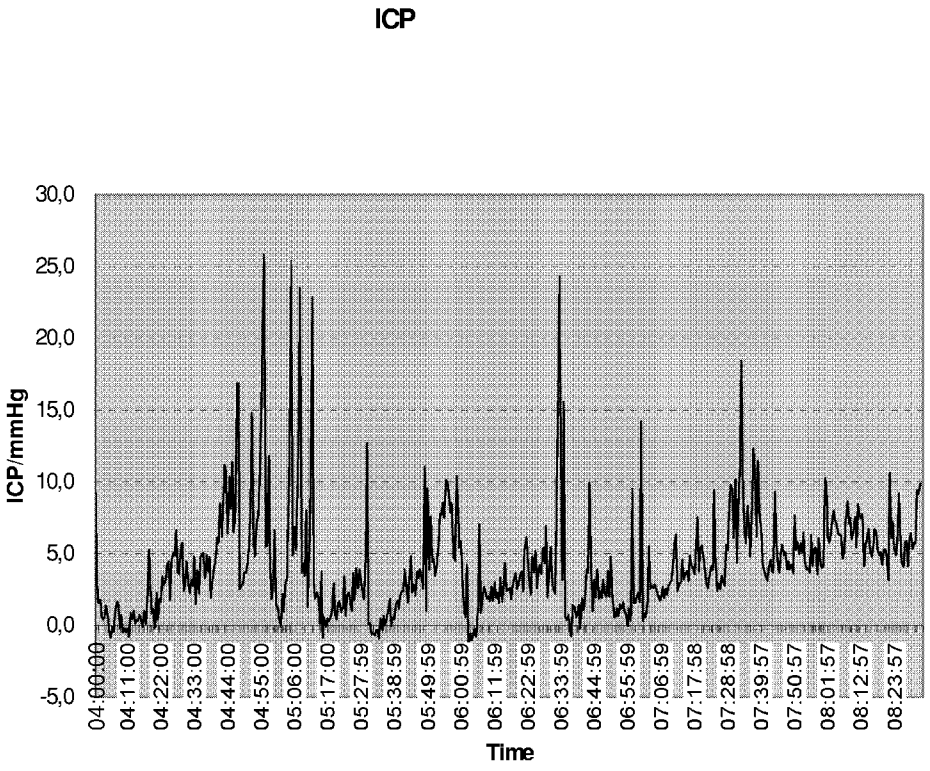
In order to measure intracranial pressure the catheter was inserted into the frontal horn of one lateral ventricle. The patients were placed in supine position on the operating table. Either general or local anaesthesia was used. After preparation of the operating field was, a short skin incision was made one inch to the right of the midline, and a 12mm burr hole was made frontal to the coronal suture. The dura was opened by cruciform incision and coagulated; the arachnoid was also sealed with bipolar coagulation.

The decision to perform a shunt operation in the study design was made according to ICP analysis only, regardless of other test results. For the ICP measurement, the basal level was set to the level of the forehead. A basal pressure below 5 mm Hg was considered normal. The ICP was considered abnormally

high if it was continuously above 10 mm Hg, or if the basal pressure was between 5 and 10 mm Hg and there were any A -waves or more than 30% B -waves during the recording period. Continuous ICP of 20 mm Hg or more excluded an NPH diagnosis and was considered to be raised ICP. The ICP was recorded for 24 hours with a Datex™ transferrable monitor, connected to a PC computer. The computer restored the data, which were recorded as an absolute value every 30 seconds. The data were analysed afterwards by using Microsoft Excel™ with both numerical values and figures. During the recording, the clinical status of the patients was carefully followed.

The shunt operation was ventriculo-peritoneal and was performed during the same hospital stay. We used Holter medium-pressure valves (Codman, Codman & Shurleff, Inc., Randolph, MA, USA) with an opening pressure of 40-70 mm H2O (±10 mm H2O). The routine hospital stay after the shunt operation was 4 days, after which the patient was discharged either home or to the referring hospital. The stitches were removed in the routine wound check some 10 days later in the patient's own health care unit. The patient was given written instructions in together with oral information of postoperative treatment during the hospital stay.

Figure 3. A typical ICP recording curve showing spikes and plateau waves. The patient had walking difficulties and progressing memory loss. The basal pressure is around 5 mm Hg and there are spikes with ICP as high as 25 mm Hg and a plateau -wave lasting 10 minutes, with ICP as high as 15 mm Hg at maximum. The recording was evaluated to be pathological.



⇑ ⇑

^ Plateau Spike

Plateau: rise of ICP up to 10-15 mm Hg lasting about 10 minutes

Spike: A quick rise in ICP presenting 0-2 times per minute, with ICP in this case as high as 25 mm Hg.

3.3 Pathological changes and immunohistochemichemistry

A cortical brain biopsy for neuropathological investigation from the right frontal cortex was obtained prior to inserting the ventricular catheter, in order to verify other dementating processes e.g. Alzheimer's disease. Cylindrical biopsies with a diameter of 2-5 mm were fixed in formalin and embedded in paraffin, and 5 μm thick sections were prepared for analysis. The sections were stained with Haematoxylin and Eosin (HE) and Bielschowsky silver (BS) impregnation techniques for diagnostic purposes. The classification of biopsies into AD positive or negative was based on the presence of plaques on silver staining. Counts of neuritic plaque (NP) were estimated semi-quantitatively (none or no plaques/field, some or less than 20 plaques/field and many or more than 20 plaques/field). Counts of neurofibrillary tangles (NFT) were rated identically (none, some and many/field).

Thereafter, immunohistochemical measurements were made. Employing immunohistochemical analysis, the βA4 aggregates, PHF-τ and α-synuclein expressions were visualised. Monoclonal antibody to human βA4, at a dilution of 1:100 (DAKO, M872), monoclonal antibody to human PHF-τ (AT8) at a dilution of 1:100 (Innogenetics BR-03), and monoclonal antibody to rat synuclein-1 (Transduktion Laboratories S63320) at a dilution 1:1000 were used. The βA4 expression was estimated within the total available gray matter with the βA4 load being reported as stained area fraction. The expression of the PHF-τ and α-synuclein were rated as negative or positive. These pathological analyses were performed in the Department of Clinical Pathology, Kuopio University Hospital.

3.4 MRI study

In the MRI -study, special attention was paid to the volume of the hippocampus. To further characterise hippocampal pathology in relation to the symptoms of NPH, the hippocampal volume in NPH patients was compared between subgroups in relation to increased intracranial pressure, postoperative outcome, and cortical AD pathology. The brains were scanned with a 1.5 T Magnetom (Siemens, Erlangen, Germany) using a standard head coil and a tilted coronal 3D gradient echo sequence (magnetisation prepared rapid acquisition gradient echo: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 × 192, 1 acquisition). The boundaries of the hippocampus were manually traced from coronal 2.0 mm thick slices by a single rater, blinded to the clinical data of the study subjects. The rostral end of the hippocampus when it first appeared below the amygdala was the starting point. The caudal end of the hippocampus was taken as the section in which the crura of the fornices departed from the lateral wall of the lateral ventricles. The number of voxels within the region creating the volume was calculated using in-house developed software for a standard Siemens work console.

The hippocampal measurements were not used as a diagnostic aid in the selection process of any of the study groups. To exclude confounding effects of individual and gender- related size variability, the volumes were normalised to the coronal intracranial area measured at the level of the anterior commissure (the volumes were multiplied by 100 and divided by intracranial area). The NPH group was then divided for further analyses into two subgroups according to the neuropathological findings in the biopsy, and the need for shunting.

3.5 Neurophysiology

Auditory P50, N100 and mismatch negativity (MMN) were measured using an auditory oddball paradigm with 85% of standard tones (800 Hz, duration 85 ms) and 15% of target tones (560Hz, duration 85 ms) delivered randomly with an ISI of 1 s to the right ear at 60 dB above the hearing level. The subject was instructed not to pay attention to the tones but instead to read a self-selected text.

The event related potentials (ERP) were recorded using Ag/AgCl electrodes placed on the scalp according to the International 10-20 System. Both vertical and horizontal eye movements were monitored. All electrodes were referred to the right mastoid. EEG and eye movement signals were filtered with a bandpass of 0.5-100 Hz, and digitised continuously at 256 Hz. The continuous data were transformed off-line to epochs of -100 to 900 ms relative to the onset of each stimulus. Epochs containing eye movement artefacts were rejected using both automatic and manual checking of data. The epoch transformed data were averaged and filtered digitally with a low pass cut-off frequency at 20 Hz (3 dB point of 24 dB/octave roll-off).

The latencies of averaged ERPs were measured relative to the onset of the stimuli and the amplitudes relative to the 100ms pre-stimulus baseline. A neurophysiologist who was unaware of the results of ICP recording or biopsy findings made the analysis. To test the differences in deviance detection between the groups, the subjects' averaged responses to deviant tones averaged across subjects in each group, and the standard deviations of the mean were calculated for each sample point. ERP amplitudes were measured relative to the 100-ms pre-stimulus. MMN was measured as the mean amplitude of the deviant-standard difference curve over the 100-270 ms range..

3.6 Neuropsychological evaluation

The neuropsychological test battery included 24 different tests including tests assessing learning and memory, verbal and visuoconstructional abilities, and the assessment of attention and flexibility of mental processing. A neuropsychologist who was unaware of the results of the pressure measurements and the clinical outcome performed the neuropsychological evaluation. In the final results, in the Finnish version of the verbal fluency test the scores of each letters (P, A and S) were calculated together. The test battery is presented in detail in Appendix 1. Patients underwent the tests both preoperatively and three months and 1 year postoperatively. The preoperative scores of each test were analysed, comparing the group later to be shunted versus not to be shunted. In addition, for shunted patients the pre- and postoperative scores were compared between each other.

3.7 Infusion test

In our infusion test, patients lay on their left side with an ICP -catheter already inserted into the ventricle and the measuring device calibrated. The injection site was prepared and draped to the lumbar area and a 22-gauge spinal needle was inserted between the L3 and L4 spinous processes to puncture the dural sac. Its position was checked by letting a drop of CSF from the needle. The needle was then inserted into an electrically driven infusion pump. The infused liquid was Ringer Lactate-solution™. The basic rate of 0.5ml/min and the rate is raised after every 5 minutes with a rate of 0.5ml/min. The maximum speed of infusion was set to 5ml/min. During the infusion, the clinical status of the patient was carefully followed and the ICP recorded. The rise in ICP was recorded as an absolute numerical value every minute. The infusion was continued until the patient showed clinical symptoms of raised ICP, or until the ICP -level of 30mm Hg was achieved, after

which the infusion was stopped. The ICP was lowered by letting the CSF out through the intra-ventricular catheter until the symptoms were relieved, or the ICP had fallen to the level of 10 mm Hg. The patient was excluded from the final analysis if the ICP remained below 25 mm Hg after 45 minutes of infusion. The resistance to outflow was calculated from the absolute values of ICP during the infusion test. The results of the infusion test are presented as resistance outflow (Rout) and a diagram.

3.8 Follow-up

Patients were followed at 3 months and 12 months post-operatively at the outpatient clinic (Figure 2). On both occasions, neuropsychological and neurophysiological tests and radiological examinations were repeated. The clinical condition of the patient was evaluated at the visit but was also certified from the next of kin either during the visit or by telephone later.

The follow- up of all patients finalised after five years on average by telephone or by letter. The effect of treatment on the main symptoms (memory impairment, walking disturbance and urinary incontinence, and on activities of daily living) was evaluated and compared with the status prior to pressure measurement, and was graded as follows: 1) improved, 2)no change and 3) worse.

3.9 Statistical analysis

The data were analysed by utilising SPSS for Windows 9.0 software. Student's t-test and the paired t-test were used to compare the means of the study groups. Correlations were calculated using the two-tailed Pearson's correlation test. The results are expressed as mean ± standard deviation (S.D.). The level of statistical significance of differences was defined as $p<0.05$.

3.10 Ethical review

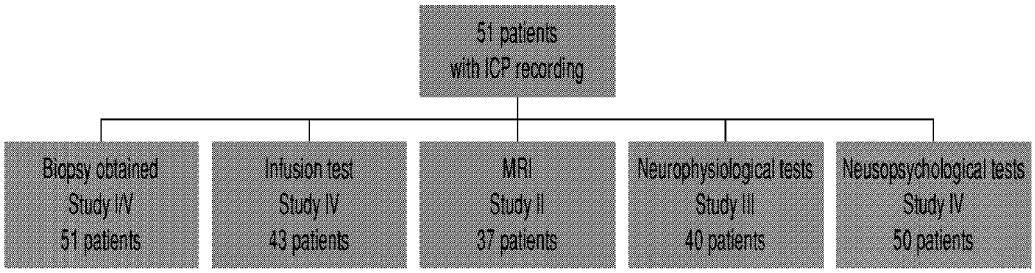
The Research Ethics Committee of Kuopio University and of Kuopio University Hospital, Kuopio, Finland, approved the study. Informed consent was required of all subjects entering the study. All had time for extended discussion with their next of kin and their doctor about the details of the study. No one refused to participate in the study.

RESULTS

1.Patients

Fifty-one NPH patients were enlisted in the prospective study group. The clinical data of the NPH patients are shown in Table 3.

Figure 4. Patients of the prospective group and their preoperative investigations.



1.1 Age and sex

In the whole study, the mean age of the patients was 66.5 years (range 29-74 years). In the 25 shunted patients, the mean age was 67.5 years (±6,7y, range 49-74 years), and in patients with no need for a shunt it was 65.6 years (±12.3y, range 29-74 years). In patients with pathological changes indicating AD, the mean age was 70.7 years (±4.7y), while in patients without those changes it was 65.1 years (±11.1y) (n.s). Of the 51 patients, 27 were men and 24 women.

1.2 Symptoms and Mini mental status examination (IV)

The main subjective complaint of the patients was memory difficulty (84%)(IV). Urinary incontinence occurred in

25 patients (49%) and gait disturbance in 41 patients (80%). All three symptoms simultaneously were seen in 23 patients (45%). Of patients with an increased pressure 11 had all three symptoms. The duration of symptoms was less than 6 months in 3 patients needing a shunt and in 6 patients not needing a shunt. Eight patients who needed a shunt and 5 patients who did not had had symptoms for between 6 months and 12 months, whereas 14 shunted patients and 15 patients with no shunts had had symptoms for over a year.

The mean value of the MMSE- score in the whole population was 22.8 (I,IV). It was 23.7 in patients who needed a shunt, and 21.9 in patients not needing a shunt(n.s.). In patients with neuropathological changes suggesting AD, the MMSE -score was 21.5 (n.s.). Besides symptoms of NPH, the patients also had radiologically diagnosed NPH.

Table 3. Baseline characteristics of the 51 patients in the prospective study.

	All	CSF shunt	No CSF shunt
Patients (N)	51	25/49%	26/51%*
Males (N/%)	27/53%	14/56%	13/50%
Mean age years	66.5	67.5	65.6*
Main symptoms			
-memory difficulties (N/%)	43/84%	21/84%	22/85%
-gait disturbance (N/%)	41/80%	21/84%	20/77%
-urinary incontinence(N/%)	25/49%	12/48%	13/50%
MMSE	22.8	23.7	21.9
Infusion test performed (N/%)	43/84%	20/80%	23/88%
AERP (N/%)	40/78%	17/64%	23/89%
MRI (N/%)	37/73%	18/72%	19/73%
Neuropsychology (N/%)	50/98%	25/100	25/96%

There were no statistically significancant differencies between groups

2.ICP and infusion test (IV)

According to 24-hour ICP recording criteria 25 patients needed a shunt. Of these 25, 2(8%) patients had high baseline levels of ICP and 11(44%) had plateau-type waves, while only 1(4%) had spikes and 11(44%) patients had a combination of two or more these.

According to the infusion test, the Rout in patients who needed shunts was 12.86 (±7.53) mm Hg/ml/min, and 10.73 (±7.09) mm Hg/ml/min (n.s.) in patients who did not (IV).

3.Pathological changes and immunohistochemistry (I,V)

In the prospective study group of 51 patients, 16 (33%) had pathological findings that showed either certain Alzheimer's disease or changes suggestive of AD. In two patients the finding suggested reactive gliosis. In the retrospective series, on the prevalence of AD in patients investigated for symptoms of NPH, there were 50 patients out of 223 (22%) with ICP recording who showed pathological changes of AD.

Of 314 patients with ICP recording, 213 patients were investigated with immunohistochemistry. βA4 protein aggregates were seen in 80 patients out of 213 (37%) investigated with this method. On the other hand, PHF-τ, which is pathogenomonic for AD was seen in 17 patients (8%). α-synuclein pathology was not seen in any of the investigated biopsies. βA4 aggregates were detected in all cases with NPs in BS impregnation. Similarly, we also noted AT8 labelled PHF-τ in all samples with NFTs in BS impregnation.

NFT's as well as PHF-τ pathology were seen only in patients with NPH, whereas NP's as well as βA4 aggregates were seen in subjects with NPH or elevated intracranial pressure.

4. Magnetic resonance imaging in diagnosis of NPH (II)

Altogether 37 patients from the prospective study group underwent preoperative MRI. During this time but outside the study investigations were made on 24 parients fulfilling clinical criteria of AD, and on 27 healthy volunteers.

The mean age of the patients with NPH, AD and healthy controls were 67.6, 68.5, and 71.1 years, respectively (n.s.). The right hippocampus was significantly smaller in the AD group than in the control and NPH groups (12.3±3.0, 17.3±2.1, 15.8±3.7, respectively; $p<.05$). The left hippocampus was significantly smaller in patients with NPH (15.2±3.4;$p<.05$)and patients with AD (11.7±3.0;$p<001$) than in the healthy volunteers (17.1±1.6). In the study group, when the volume of hippocampus was compared between those who needed a shunt operation and those who did not, the volumes of the right hippocampus were 16.7±4.2 and 15.0±3.1, while the sizes of left hippocampus was 16.1±3.6 and 14.4±3.0, respectively. The differences were not significant.

In patients with both NPH and pathological AD changes the volume of the left hippocampus was 13.8±4.2 and right hippocampus 14.8±4.5. Difference is not significant.

When volumes of hippocampi were compared in correlation to positive recovery after shunt surgery, the only remarkable finding was in cases with memory impairment. The right hippocampus was smaller in preoperative measurement in that group of patients who improved in the memory status than in those who did not; right 16.9±2.2 (improved) and 19.9±4.1 (no change)($p<.05$), left 16.2±2.9 and 17.8±2.1, respectively. In other subgroups, there were no significant differences in hippocampal volumes.

Table 4. Hippocampal volumes measured with MRI in healthy volunteers, in patients with clinical AD and in patients in the prospective study group (88 patients).

	HV	AD	NPHall	NPHAD+	NPNnonAD
N	27	24	37	12	25
HDX	17.5±2.1	12.3±3.0 *	15.8±3.7	14.8±4.5	16.2±3.2
HDSIN	17.1±1.6	11.7±3.4 *	15.2±3.4	13.8±4.2	15.9±2.7
MMSE	28.3±1.4	21.9±6.9	22.5±5.0	21.6±6.9	23.0±3.9

* P<.05

HDX = Size of right hippocampus

HDSIN = Size of left hippocampus

MMSE = Mini Mental Status Examination

CG = Healthy volunteers

AD = Patients with Alzheimer's disease

NPH = Normal pressure hydrocephalus, all patients

NPHAD+ = NPH patients with cortical AD pathology

NPHAD- = NPH patients with no cortical AD pathology

5. Neurophysiological measurements in diagnosis of NPH (III)

Altogether 40 patients out of 51 patients were enrolled in the study groups that underwent ERP investigations. The reasons why not to all the patients were enrolled in the study were: 2 patients refused, there was lack of co-operation in 1 case and there was either overbooking of equipment or invalid data in 8 cases.

Sixteen patients who needed a shunt operation and 23 who did not a had ERP. Of those 23 patients who did not, 12 had AD pathology verified with biopsy. The latencies of P50 and N100 deflections were significantly shorter in patients with verified AD pathology than in patients without it (P50 AD:47.60±1.86 -and shunted:54.06±2.53¸non shunt: 60.19±2.35) (N100 AD:102.95±2.26, shunt 109.79±2.62, no shunt:112.46±2.40), whereas the amplitudes and deviant tones were increased.

6. Neuropsychological testing in diagnosis of NPH (IV)

In the pre-operative stage, 50 patients were investigated with a neuropsychological test battery. Thirteen of our 24 separate neuropsychological tests were taken by at least 41 (80% of total) patients. Thirteen patients were not able to perform the final analysis one year post-operatively, of whom 9 did not need a shunt. The reason why the final test was not performed (one year postoperatively) was deterioration in 10 cases, 7 of whom had Alzheimer's disease, there were 2 withdrawals, and one patient had died. The only test preoperatively which showed a significant difference between patients who needed shunts and who did not was the recognition of words -test. The MMSE-test score was 23.7 in patients with NPH and 21.9 in patients who did not (n.s.).

7.Outcome of patients with NPH (IV)

All 51 patients were reached for clinical examination 3 months postoperatively, and 50 patients after one year postoperatively: one had died 3 months postoperatively from complication after treatment for pulmonary embolism. Information about all patients was obtained for five-year postoperative examination. Altogether 34 patients were alive and 17 dead (8/32% shunted and 9/35% non-shunted). The overall outcome is shown in Table 5.

Table 5. The overall outcome of the 51 NPH patients at different stages of follow-up: 25 patients were treated with a CSF shunt, and 26 were not.

	3months with shunt 25 pts	1year with shunt 25pts	5 years with shunt 25pts	3months without shunt 26 pts	1year without shunt 26pts	5 years without shunt 26pts
Better	21	18	9	7	7	-
Unaltered	1	1	5	8	7	8
Worse	3	5	3	11	12	9
Dead		1	8			9

Table 6. The effect of shunting on subjective clinical symptoms of survived patients in different stages of follow-up (25 patients).

	Better	Unchanged	Worse
Urinary incontinence			
3 months (12 patients)	7/58%	3/25%	2/17%
1 year (11 patients)	7/64%	2/18%	2/18%
5 years (7 patients)	2/29%	4/57%	1/14%
Gait			
3 months (21 patients)	16/76%	3/14%	2/10%
1 year (20 patients)	12/60%	5/25%	3/15%
5 years (15 patients)	7/47%	5/33%	3/20%
Memory			
3 months (21 patients)	10/48%	8/38%	3/14%
1 year (20 patients)	9/45%	5/25%	6/30%
5 years (13 patients)	5/38%	4/31%	4/31%

Three months after shunt placement, 16 (76%) of those 21 patients who had a walking disability preoperatively had a positive result, while for urinary incontinence and memory difficulties the figures were 7/12 (58%) and 10/21 (48%), respectively.

Of the 25 patients who had a shunt implanted, 24 were still alive 12 months after operation. Twelve of the 20 living patients with preoperative gait disturbances still benefited from the shunt, and 7 (64%) of the 11 patients who had urinary incontinence felt better ($p<.01$). On the other hand, only 9 patients of 20 (45%) (n.s.) with memory disturbances had improved clinically one year post-operatively.

In the final stage 5 years after the shunt operations, 8 of the shunted patients of and 9 of the non-shunted had died, one of them already 3 months after operation. Seven patients were still walking better 5 years after operation, while 5 were unchanged and 3 felt worse than before operation. The figures for memory impairment were: 5, 4 and 4,

respectively. One patient with no clear memory disturbance felt subjectivelly better at this stage.

Urinary incontinence was better in 2 patients 5 years post-operatively, whereas in 4 it was unchanged, and 4 felt the incontinence was worse than in the preoperative phase.

In activities of daily living, 18 of 25 (72%) patients who had had a shunt operation managed better post-operatively, while 7 were the same as preoperatively or worse. Two of the 7 patients had Alzheimer's disease. Five years post-operatively, 13 (77% of 17 alive) patients with a shunt were able to manage life independently, while of those with no shunt 9 (53%) were able to, and 3 (18%) needed help.

Of the 16 patients who had pathologically verified Alzheimer's disease, 7 coul manage independently life in the pre-operative phase and 4 were institutionalised. After 5 years of follow-up, the same figures were 7 and 2, respectively. Four (25%) of them had died. One of the 2 patients who had both high ICP and Alzheimer's disease lived at home, managing independently, while the other one was institutionalised. In the follow-up, their independence of care did not change.

Shunting did not have any effect on any of the paramaters measured by neuropsychological tests, when compraing preoperative results with those at 12 months.

DISCUSSION

1.ICP

In our study the diagnosis of NPH was based on ICP-recording. We decided in the study design to use ICP as the reference for the diagnosis of NPH. This method is said to be the golden standard (104, 141, 148). We measured ICP for 24 hours, which is generally considered to be long enough in diagnosing pressure waves. We performed pressure recording intraventricularly, which is a reliable method (141, 148), but intrathecal measurement has also been used (144), and is less invasive, but according to Pisani may not be accurate enough . In this substudy we did not have any haematomas or infectious complications.

We have concluded that ICP seems to be the test of choice in diagnosing NPH. ICP recording has many advantages, e.g. it measures directly the pressure in the ventricles. The possibility of obtaining a biopsy simultaneously was the other advantage of our method. We have compared the other diagnostic tools, evaluated during this study with this standard.

2.Infusion test

Various methods of carrying out infusion tests have been presented since Katzman's constant intrathecal infusion (23, 59, 60, 92). In our infusion test we modified this infusion technique as we raised the speed of infusion every 5 minutes. We wanted to get the results more rapidly than in previous tests (23, 60, 92), to decrease the risk of infection. In our study, the Rout of the patients who needed shunts was 12.86 (±7.53)mm Hg/ml/min while in patients who did not it was 10.73 (±7.09)mm Hg/ml/min(n.s). These figures are similar to those presented in previous reports, in which the limit for performing shunt Rout was set to level ≥12mm Hg/ml/ (18)and

≥10mm Hg/ml/min (98). On the other hand, this method was a bit different from those methods reported before. We did not find the same diagnostic value of infusion test as Borgesen and co-workers and Malm and associates found (22, 23, 114). But, the diagnostic value of reported methods have varied, and no absolute numerical level to set the diagnosis has been agreed on.

In patients needing a shunt there was a slight tendency towards faster rise in ICP during the infusion test, but the difference was not statistically significant.

3.Pathological changes and immunohistochemistry in NPH referring to Alzheimer's disease

The patients referred to us had different combinations of symptoms suggesting NPH, Especially memory disturbance was difficult to evaluate quantitatively, the main cause of it in elderly people is AD. However, this diagnosis, when based on ante mortem studies, should be made with caution (151). NPH is almost impossible to differentiate clinically from AD. In our retrospective report we had a total number of 50 patients out of 223 (22%) who had neuropathological changes of AD either in a clinical stage or imminent. In our prospective group, in which all patients were biopsied, the prevalence of changes indicating AD was as high as 31.3% (16 of 51 biopsied). Bech and co-workers reported (8) AD changes in 6 out of 27 NPH patients (22%), whereas Golomb et al (65) showed in their series of 117 brain biopsies that 6% of NPH cases fulfilled CERAD criteria (56) for definite AD. Our results indicate much higher incidence of AD pathology in NPH material.

The incidence of AD in patients with suspected NPH is 33%-50% depending on the age group and the strictness of the exclusion criteria. The upper age limit in our prospective group was 75 and the youngest patient was 29 years old. The probability of AD or a combination of AD and NPH increases with

age, which should be born in mind when dealing with dementing processes in patients who are older than those in our study as the incidence of AD and the density of lesions (NP) increases with age (9, 17, 25, 42, 156). We also noticed this phenomenon among our elderly patients, who were in the retrospective study or those excluded from the prospective study because of high age (33%-50%).

According to definitive immunohistochemical criteria, 8% of our NPH patients had Alzheimer's disease, their PHF-τ and Aβ values were positive, which is of about the same proportion as in earlier reports (8, 65), in which the proportion of AD patients is 4-6%.

Immunohistochemical techniques seem to be more sensitive than morphological techniques in the evaluation of lesions suggesting AD. In an earlier report by Bech and co-workers (8), 22% of patients had morphological changes of AD and when studied immunohistochemically as many as 38% had changes suggesting a very high risk of developing the disease.

Most of the patients with AD had no increase in ICP. Two patients of our prospective study group had both raised intracranial pressure and AD. These patients, after shunting, had poor outcome.

The antibody used in this study is considered to be the one, which can identify tangles in a very early stage of their formation, whereas silver stains only visualise the fully formed tangles. Similar difference was found when comparing the estimation of plaques.

We took our biopsies through the right frontal burr hole from the posterior premotor frontal cortex. This localisation is considered to be accurate enough to differentiate AD from NPH. According to Silverman et al. and Bennett et al. the density of lesions (NP) increases with age, and the lesions are most commonly situated in the frontal and temporal lobes (9, 156).

A good reason for unsuccessful shunting in many earlier N clinical NPH series reported (147, 170) may be that many patients had a combination of AD and NPH.

4.Value of MRI in diagnosing NPH

In earlier studies the size of the hippocampus has been found to decrease after traumatic head injury. The size of the hippocampus has been studied in relation to recovery of memory problems (12), AD, vascular dementia and Parkinson's disease (102, 103). In our study the volumes of both hippocampi were measured in patients with a suspicion of NPH on clinical and CT grounds and compared with changes in patients having clinical AD and in normal volunteers. In this study the volumes of hippocampi were significantly smaller in the patients with clinical AD. Slightly smaller left hippocampi were seen in patients with NPH than in normal volunteers.

Patients with AD had significantly smaller hippocampi than those with NPH. Because the ventricles may be enlarged in both AD and NPH the hippocampal volume may help in making the diagnosis.

In our total study group the size of the hippocampus did not differ in patients who needed a shunt from those who did not. According to these results, the diagnosis of NPH can not be based on the grounds of hippocampal volumetry but this procedure may help in evaluating elderly patients for invasive studies.

We did not find a direct correlation between the volumes of hippocampi in the postoperative recovery phase. The right hippocampus was actually bigger in non-responders. In a previous study, the volumes of hippocampi were significantly smaller in patients having memory difficulties (63, 64). There was no biopsy verification for other dementing processes in those patients. In our NPH study patients who had pathological changes of AD showed smaller volumes of hippocampi, but these changes were not significant.

Hippocampus volumetry seems to be a useful tool in distinguishing patients with already clinically advanced AD as a part of etiological investigations in examining patients with memory impairment. It does not differentiate early NPH and AD.

5.Neurophysiological studies

A prolonged auditory stimulus gives evoked response in the human brain, which is highly constant and reproducible (77). We performed auditory event-related potentials on patients with suspected NPH.

We observed increased amplitudes and shortened latencies in the auditory components of P50 and 100. This finding is, to our knowledge, the first of its kind. This result is somewhat unexpected, since in earlier reports the latencies of AERPs have been shown to increase in degenerative situations (132). Lesions of frontal lobes also reduced attention-related negativity and to cause impaired behavioral performance.

Also, we saw a clear decrease in the size of automatic stimulus detection (MMN). A decrease in MMN has been reported earlier in Parkinson's disease (136) as well as in ageing and AD (135). This may be related to the hearing process and shows impaired auditory discrimination. Our results suggest that automatic stimulus detection is impaired in patients with concomitant NPH and AD, and that it has clinical value in differenting these patients from the patients with NPH alone.

6.Neuropsychology

MMSE is a simple bed-side tool in diagnosing dementia (49, 68). In our patients, the MMSE score did not differ significantly between patient groups having NPH with or without AD and those who only had symptoms of NPH without a raise in ICP. This may be because the patients who had symptoms which are similar in both diseases were in the pre-clinical phase of

the disease (88). We did not repeat the MMSE during the follow -up and do not know if there were any later changes in the results of this test.

Only a few studies included neuropsychological tests in the diagnosis of NPH. Gustafsson and Hagberg (72) noticed that careful psychometric tests should be made to diagnose hydrocephalic dementia, whic they think is essential for good recovery from shunt surgery. Graff-Radford and co-workers (68) used a large range of tests in patients with NPH. They did not correlate any test to the need for surgery. Besides MMSE, we used a wide battery of various neuropsychological tests. However, only one test,the word-recognition -test, showed any difference in patients who needed of shunt from those who did not. This single test cannot be alone diagnostic in patients with symptoms of NPH. The lack of neuropsychological changes is somewhat surprising, as one of the main symptoms of NPH in our study group were memory difficulties. The tests were validated, so we did not compare the results of these tests with those of a normal control population. Some of the tests seem to be quite difficult to taken by elderly people, which, of course, decrease their diagnostic value.

In this study, neuropsychological tests were not of value in diagnosing NPH in patients with symptoms of NPH, nor did they correlate with clinical outcome after shunting. The same difficulty in differentiating patients' outcome with sophisticated neuropsychological tests has been shown in younger patients after recovery from subarachnoidal haemorrhage (97).

7.Outcome of NPH

7.1 Clinical outcome

We had a five-year -follow-up in our patients with NPH. In the present study, improvement in activities of daily living was achieved in 72 % of shunted patients, which is quite similar to that of Larsson's 74% rate of success (107).It has been claimed that the prognosis for gait disturbance before mental deterioration is more favourable than that for early mental symptoms (69), although conflicting opinions have been published (107). The order of appearance of symptoms was not investigated in our study. On the other hand, long duration of dementia correlates negatively with outcome (70). Larsson noticed that the duration of symptoms should not deter the treatment of a patient with a shunt (107).

Patients with the complete clinical triad are most likely to respond to surgery (72, 107). Gait disturbance frequently responds whereas impairment of cognitive functions has the worst outcome. This was also the case in our study. Almost half of those patients who were alive 5 years postoperatively felt their gait to be better than in the preoperative stage. One reason for not having an even better result may be that the patients may have some other undiagnosed neurodegenerative disease.

The recovery rate in memory impairment was 48% after 3 months, but it decreased to 45% in 1 year. After 5 years of follow-up, the rate of success was only 29%. Our patients did not improve in their memory functions as well as did patients in previous studies (70, 72, 168).

In our series, 78% of patients with walking disability was better after 3 months and the positive effect of shunt surgery remained for at least 1 year. However, the recovery rate after 5 years was only 41%. In Larsson's series, recovery took place in 78% of cases (107), while a recovery rate as good as 95% has been reported by Raftopoulos (147).

Regarding urinary incontinence, a positive effect was seen in 58% of our patients 3 months after shunt surgery. Five years after shunt surgery, 29% of patients felt this symptom was better. The recovery rate after 3 months was of the same magnitude as in previous studies (147).

7.2 Neuropsychological recovery

The mean preoperative MMSE-score was as high as 22.8 in 16 patients with neuropathological changes of AD. This suggests that in many of those patients the disease was in the pre-clinical phase and little neuropsychological change could be seen even after one year of follow-up. We did not repeat this test in postoperative follow-up. Instead, we used a thorough neuropsychological test battery to follow-up the objective recovery.

There are a few studies on neuropsychological improvement after shunt placement (72, 107, 147, 169). Tromp and co-workers (169) investigated 30 patients with NPH. They found that a spinal tap had no influence on the cognitive functions. Three months after surgery, operation had noticeable effect only on attention. In many series, there has not been any improvement in neuropsychological tests. Graff-Radford and co-workers analysed neuropsycholgical tests as well as other parameters (68). None of their tests showed significant improvement even though the visual naming -test had some prognostic value. Neuropsychological improvement was seen in 66.6% of cases in Raftopoulos' series (147). On the other hand, 5 of their 23 patients deteriorated and one died. We did not find significant improvement in any of the neuropsychological tests. although the patient felt subjectively better.

8.CONCLUSIONS

On the basis of our data, the following conclusions can be drawn.

1. The prevalence of Alzheimer's disease in patients who have symptoms of normal pressure hydrocephalus is high. Altogether 22% of our patients had histopathological changes indicating Alzheimer's disease. In the prospective study group the prevalence of Alzheimer's disease in patients with symptoms of normal pressure hydrocephalus was 33%. Cortical biopsy combined with intracranial pressure recording improves the diagnostic accuracy and helps in explaining the unsuccessful response to shunt surgery. Immunohistochemistry further increases the diagnostic accuracy of Alzheimer's disease, and shows that there is up to 38% risk of patients with symptoms of normal pressure hydrocephalus developing Alzheimer's disease at some stage of life. Also, according to immunohistochemisty, 8% of patients with NPH have Alzheimer's disease.

2.Measurement of hippocampus volumes can distinguish patients who have clinical Alzheimer's disease from patients who have early normal pressure hydrocephalus. However, it does not help in identifying patients who should be shunted, although they have symptoms of NPH.

3. Auditory evoked response potentials (AERP) can identify patients with normal pressure hydrocephalus and concomitant Alzheimer's disease pathology. Its full clinical value in the differential diagnosis of Alzheimer's disease and possible normal pressure hydrocephalus needs further investigation.

4. Neuropsychological tests are of hardly any value in diagnosing normal pressure hydrocephalus. In this study, the tests results did not show any significant improvement after shunt operation, even when the patients felt subjectively

better. MMSE is of no help in diagnosing early normal pressure hydrocephalus, although it can be used to identify patients with memory problems.

5. The prognosis of normal pressure hydrocephalus after shunt operation is good. About 75% of patients have good recovery and improved quality of life. The best effects of shunts are on urinary incontinence and gait disturbances. Impaired memory seems to have little capability of recovery. The general improvement continues for up to 5 years. After 1 year postoperatively, 64% of patients walked better and 45% had subjectivelly better memory than preoperatively. Five years post-operatively, 47% of shunted patients walked better and 38% of patients felt their memory was better than preoperatively.

Our findings show that the 24-hour intracranial pressure recording seems to be adequate test in diagnosing normal pressure hydrocephalus and in positive cases quality of life improved in more than half of the patients even though mortality did not decrease after shunt surgery in 5-year follow-up.

Appendix 1

Neuropsychological evaluation

The cognitive tests selected were designed to measure neuropsychological functioning in four major areas:

1.Learning and memory.

Memory was tested using the following tests:
The story recall test from Wechsler´s Memory Scale was used to assess episodic memory. A paragraph of 23 verbal ideas was read by the examiner, and immediate and delayed recall after 1 hour delay filled with other neuropsychological tests were assessed. The score is the sum of ideas recalled immediately and after the delay.
The learning of word list (modified from the Auditory-Verbal Learning Test) was used to examine verbal learning, delayed recall and recognition. Ten words were read aloud 4 consecutive times. After each presentation, an immediate free recall of the words was elicited. The delayed recall of words was assessed after 1 hour. The delayed recall was immediately followed by the delayed recognition task, in which subjects were asked to indicate the words of the original list from a list of 30 words read aloud to them. The score for the word list test is the total number of all words repeated during 4 trials, for maximum span for longest list the patient could remember of 10 words, and for intrusions the number of words the patient produced but which had not appeared in the Word List. The score for delayed recall is the number of words recalled after the delay and the score for recognition is the number of correctly recognised words.
The memory for designs test from Wechsler´s Memory Scale was used to evaluate memory for nonverbal, visuospatial material. It consists of four geometric-type designs that subjects are allowed to study for 10 seconds and then required to draw from

memory. The delayed recall was elicited after 1 hour. The scoring was made according the Wechsler Memory Scale Manual.

Immediate verbal memory and verbal attention span was measured by using standardised versions of the Digit Span Forward and Backward test. The score is the length of the longest correctly repeated number sequence.
For analogous assessment of visuospatial short-term memory and attention span, The Corsi Block Tapping Task was used, this test was made forward only.

2.Visuoconstructional ability

Visuoconstructional abilities were assessed using the Block Design test from the Wechsler Adult Intelligence Scale-Revised, which is a standard clinical tool for detection of visuospatial and constructive impairment. The score is the raw score of the correctly solved items.

3.Verbal ability

The Vocabulary test from the Wechsler Adult Intelligence Scale-Revised (34) was used to assess general verbal activity. The test was administer in split halves, starting alternately with part A and part B. The score is the sum of the correct answers multiplied by two.
The Finnish version of the Verbal Fluency -Test on letters was used to evaluate word fluency and retrieval from semantic memory. The subjects are given 60 seconds to produce as many words as possible beginning with each of the letters P, A, and S, excluding proper names or different forms of the same word. The Verbal Fluency Test on category requires producing as many animal names as possible in 60 seconds. The score is the total number of correct words produced for each letter or category.

4.Attention and flexibility of mental processing

The Stroop Test was used to evaluate sustained attention, resistance to interference and response inhibition. In form A, the subjects are asked to read aloud 50 colour names (red, blue, green etc) printed in black, and in form B to state the colour of 50 coloured dots. In form C, the subject is asked state the colour of 50 words printed in a colour different from the word itself (interference condition). The scores are the time used to complete each task.

The Trail Making Test was also used to evaluate sustained attention, resistance to interference and response inhibition. In part A, the subject is asked to draw a line connecting consecutively -numbered circles. In the modified version of part B, subjects have to draw a line alternating between numbers and the names of the twelve months. The scores are the time to complete each task.

The Letter Cancellation task requires visual selectivity at fast speed on a repetitive motor response task. Visual scanning and activation and inhibition of rapid responses are needed in this task. The test sheet contained 20 rows, each containing 40 different letters, and the task was to strike out a certain letter as accurately and quickly as possible. The score is the number of letters correctly found in 60 seconds.

The Alternating S-test was used to evaluate the flexibility of mental processing. The subject was asked to write the letter S repeatedly for 30 seconds, and the reversed letter S for 30 seconds.

Then the subject was asked to write the letter S and the reversed letter S alternately for 60 seconds. The score is the sum of correct items. The Modified finger-tapping test was used to assess simple psychomotor speed. Tapping rate was determined over 10 seconds in two trials for each hand. The score is the mean of both hands.

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