Use of MR Perfusion Imaging to predict treatment effects in patients with Idiopathic Normal Pressure Hydrocephalus

Degree project thesis in Medicine

Anna Bogdanoff

Mats Tullberg

Jonathan Arvidsson

Doerthe Constantinescu Ziegelitz

Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden AND
Department of Clinical Neuroscience, Institute of Neuroscience and Physiology,
Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

UNIVERSITY OF GOTHENBURG

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Abbreviations

AIF - Arterial input function

BD - Binswanger´s disease

B-waves - A defined type of variation of the intracranial pressure

CA - Callosal angle

CBF - Cerebral blood flow

CNS - Central nervous system

CSF - Cerebrospinal fluid

CT - Computerized tomography

CVR - Cerebrovascular reactivity

DESH - Disproportionately enlarged subarachnoid space hydrocephalus

DSC MRI - Dynamic susceptibility contrast magnetic resonance imaging

DTI - Diffusion tensor imaging

DWI - Diffusion weighted imaging

ELD - Extended lumbar drainage

EPI - Echo planar imaging

FLAIR - Fluid-attenuated inversion-recovery

ICP - Intracranial pressure

iNPH - Idiopathic normal pressure hydrocephalus

IQR - Interquartile

M1 – Medial Cerebral artery segment one

M2 – Medial Cerebral artery segment two

MRS - Magnetic resonance spectroscopy

rCBF – Relative cerebral blood flow

r_s - Spearman correlation coefficient

Rout - Resistance to cerebrospinal fluid outflow

ROI - Regions of interest

Abstract

Title: Use of magnetic resonance imaging to predict treatment effect in patients with Idiopathic Normal Pressure Hydrocephalus.

Author, year: Anna Bogdanoff, 2018.

Institution, city, country: Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden AND Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Background: Idiopathic normal pressure hydrocephalus (iNPH) is a neurological disease characterized by disturbed cerebrospinal fluid dynamics that result in ventricular enlargement although the intracranial pressure remains normal. The disorder causes gait, balance, cognitive and urinary dysfunction and is one of few causes of treatable dementia. More than 80 % of the patients improve clinically after neurosurgical treatment with peritoneal- or ventriculo-artrial shunt. However, reliable markers for diagnosis and prediction of outcome after shunt surgery are lacking. There is a general agreement that cerebral blood flow (CBF) changes play a central role in the pathophysiology and in association with clinical symptoms. Perfusion patterns that predict good shunt outcome has not yet been identified.

Aim: To investigate whether periventricular perfusion changes, measured with magnetic resonance imaging (MRI), can predict the effect of shunt treatment in patients with iNPH.

Methods: Prospective, observational study with 24 consecutive patients (median age 76). The participants were all diagnosed with iNPH according to international

guidelines and subjected to shunt surgery. All patients underwent preoperative examination of clinical symptoms and a four-month postoperative follow-up. Perfusion evaluations were based on regions of interest analysis.

Results: No significant correlation could be found between preoperative periventricular CBF and preoperative clinical performance or postoperative clinical improvement. The CBF did not differ between shunt treatment responders and non-responders. However, a linear relationship was observed comparing the pre- and postoperative CBF in six patients available (p=0.03). Unexpectedly, comorbidity was associated with a poor clinical improvement after shunt treatment (p=0.006).

Conclusion: This study could not show a predictive value of periventricular perfusion with regard to outcome after shunt surgery. The results may support our hypothesis of a relationship between improved periventricular perfusion and clinical improvement. However, statistical power is lacking due to the small sample size. Further studies with larger sample sizes are warranted.

Key words: Idiopathic Normal Pressure Hydrocephalus, MRI, perfusion

Introduction/Background

Anatomy

The cerebral ventricles are connected and filled with cerebrospinal fluid (CSF) and entitled according to position, named first to fourth according to their position. The first and second ventricle, also known as the two lateral ventricles, lie within each cerebral hemisphere. Their ventral surface are defined by the basal ganglia, their dorsal surface by the corpus callosum and their medial surface by the septum pellucidum. Furthermore, the third ventricle form a space in the midline between the left and right thalamus, connecting the lateral ventricles through the so called interventricular foramen. The third ventricle runs through the midbrain caudally to the cerebral aqueduct which opens into the fourth ventricle. This ventricle is positioned between the dorsal side of pons and ventral side of cerebellum. It narrows caudally to form the central canal of the spinal cord (1).

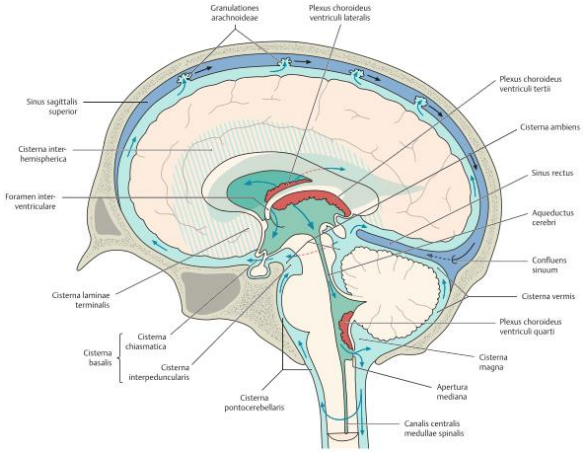

Figure 1. *Circulation of cerebrospinal fluid (1)*

Cerebrospinal fluid

The CSF bears up the weight of the brain and spinal medulla. It also serves as a mechanical protection of the central nervous system (CNS) from trauma effects, a variable in the intracranial pressure (ICP) regulation and preserves a balanced chemical environment for the CNS (2).

It is generally believed that the CSF is mainly produced by the choroid plexus, a specialized epithelium, located in all ventricles which form an interface between the blood line and the CNS (3, 4). The cardiac cycle and rapid respiratory waves promote the CSF net flow which circulates from the lateral ventricles through the interventricular foramina into the third ventricle and further through the cerebral aqueduct into the fourth ventricle. The CSF then passes through the midline aperture into the cisterna magna and into the pontine cisterns via the lateral apertures. Some of the CSF extend caudally from the basal cisterns into the spinal canal. The remaining CSF continues to flow into the subarachnoid space around the brain towards the superior sagittal sinus absorbed by specialized structures called arachnoid granulations (2).

The normal CSF volume in adults is about 150 ml and the turnover rate is between three to five times per day. Aging leads to increased CSF spaces due to loss of brain parenchyma, degeneration of the choroid plexa as well as the arachnoid granulations and the turnover rate decreases (2).

Idiopathic normal pressure hydrocephalus (iNPH)

Definition, prevalence and incidence

Idiopathic normal pressure hydrocephalus (iNPH) is a condition of the elderly of unknown cause with an idiopathic dilatation of the ventricular system without intraventricular obstruction or increased ICP. It is clinically characterized by subcortical symptomatology that generates a slowly progressive impairment of gait, balance, cognition and continence (5).

The prevalence in Western Europe is around 2 % in adults > 65 year and 6 % > 80 year (6). The operation incidence is about five surgeries/100 000/year which results in an underdiagnosed and undertreated disease (7).

Pathophysiology

The cause of the normal pressure hydrocephalus is considered to be a reduction of the cerebrospinal fluid absorption to the blood in arachnoid granulations in the sagittal sinus and along the spinal canal nerve roots. In over 50 % of the cases etiology remains unknown, therefore called iNPH.

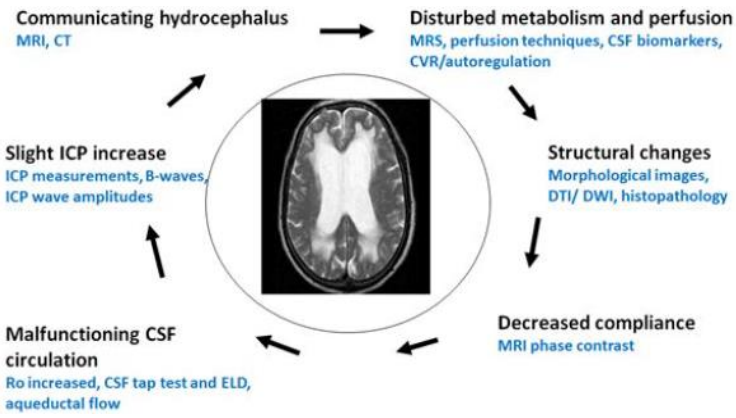

Figure 2. *Pathophysiological aspects of iNPH (Courtesy of Prof. Wikkelsø). For abbreviations please see page four.*

Cerebrovascular risk factors seem to be involved in the pathophysiology of iNPH. Jaraj et al (8) proposed that history of hypertension, diabetes mellitus and white matter lesions are related to clinical and imaging features. Israelsson et al (9) support this hypothesis claiming that vascular risk factors and vascular diseases contribute to the development of iNPH. Additionally, there is a general agreement that reduced cerebral blood flow (CBF) plays a central role in the pathophysiology of iNPH. Studies have shown that subcortical hypoperfusion, especially in the periventricular tissue, is an important contributor (2). The subcortical impact of CBF changes correspond to the subcortical clinical picture (10) but the relationship between the perfusion level and the severity of clinical features of iNPH is not clarified (2).

Cerebral changes connected to normal aging, the overrepresentation of cerebrovascular disease and vascular risk factors and the coexistence of other disorders, for instance Alzheimer´s disease, complicate understanding of the disease process (11). Figure 2, created by Professor Carsten Wikkelsø, illustrates potential pathophysiological mechanisms.

The remaining cases of NPH, called secondary normal pressure hydrocephalus, result from circumstances such as subarachnoid bleeding, head injury, infections or neurosurgery.

Clinical picture

iNPH occurs in adults at all ages but it is most common in 65-75 year-olds. Men and women are equally affected (12). The first symptom of iNPH is often disturbance of gait illustrated as hypokinetic, short broad-based steps with low foot-floor elevation, outward rotation of the toes and occasional freezing (13, 14). Other motor functions are also impaired which can cause for example brady- and hypokinesia of the face and upper extremities (15, 16).

Imbalance and postural difficulties are often experienced as a tendency to lean or fall backwards. This is related to an abnormal subjective visual vertical perception (17). iNPH patients often demonstrate emotional-motivational problems such as emotional indifference, lack of drive and apathy and/or somnolence-sopor-coma disorder characterized by for example impaired wakefulness. Among some patients an astheno-emotional disturbance with fatigue, memory- and concentration difficulties and irritability occur. Patients often experience memory disturbance (18).

Lower urinary tract symptoms such as urinary urgency, incontinence and increased frequency of urination generally develop later than other symptoms in iNPH patients, or not at all. Incontinence and urinary frequency are the main lower tract symptoms (LUTS) which most likely derive due to detrusor hyperreflexia (19).

Important differential diagnostic diseases are Binswanger´s disease, atypical Parkinson´s disease for example Progressive Supranuclear Palsy and Alzheimer´s disease due to clinical and radiological similarities such as central atrophy with dilatation of the ventricular system.

Clinical investigation

The diagnosis of iNPH is confirmed after a clinical evaluation, neuroimaging and a physiological data investigation. The European-American guidelines are often used for diagnostic criteria (20), summarized in table 1.

The general impairment in iNPH patients pre- and postoperative can be graded by a number of clinical scales. Hellström et al (21) proposed a new scale in an attempt to standardization, where the clinical performance of iNPH patients is estimated in four domains which illustrate the most characteristic features of the disease – gait, balance, neuropsychology and continence – as well as in total.

Imaging of iNPH is mainly performed by brain computerized tomography (CT) and magnetic resonance imaging (MRI). MRI is superior to CT as it provides more information of diagnostic relevance and avoids exposure to ionizing radiation. In addition, MRI is a better method for detecting white matter changes, for identification of non-communicating cases and for examination of CSF flow. Imaging criteria are

shown in table 1. Evan´s index is used to differentiate normal and enlarged ventricular size in iNPH patients (>0.3) which defines the ratio of the widest diameter of the frontal horns to the widest diameter of the brain on the same axial slice (20). Further changes that point toward an iNPH diagnosis are periventricular white matter changes, dilated temporal horns, dilated third ventricle and no cortical atrophy.

The callosal angle (CA), the angle between the lateral ventricles viewed on a coronal image, is considered to be a diagnostic tool. In individuals without iNPH the angle is between 100-120° whereas in patients with iNPH it is 50-80° (22). Furthermore, disproportionately enlarged subarachnoid space hydrocephalus (DESH) can also be a useful tool when diagnosing iNPH (23).

Table 1. *Summary of diagnostic criteria of iNPH according to the European-American guidelines (20).*

	Probable iNPH	Possible iNPH
Clinical history	Insidious onset of symptoms; after age of 40 y; duration of at least 3 to 6 m; no known cause; progressive over time; absence of other conditions that might explain symptoms	May have a subacute or indeterminate onset; begin at any age; have lasted less than 3 m or indeterminately; follow conditions that are unlikely causally related; non- or not clearly progressive; not entirely attributable to other conditions
Clinical findings	Impaired gait/balance (mandatory) combined with either or both of disturbed cognition and continence	Incontinence and/or cognitive impairment in the absence of a gait or balance disturbance; Alternatively; gait disturbance or dementia alone
Imaging	EI > 0.30, not entirely caused by atrophy; No obstruction to CSF flow; One of the following supportive features 1. Enlargement of temporal horns not entirely caused by hippocampus atrophy 2. Callosal angle ≥40 degrees 3. Altered periventricular water content not attributable to arteriolosclerosis or demyelination 4. Flow void in aqueduct or 4th ventricle	EI > 0.30; No obstruction to CSF flow; Cerebral atrophy potentially explaining ventricular size; Structural lesions potentially influencing ventriculomegaly are accepted
Physiological data	CSF opening pressure of 5–18 mm Hg (or 70–245 mm H2O)	Opening pressure measurement not available or pressure outside the range of probable INPH
Improbable or unlikely iNPH: 1. No ventriculomegaly 2. Increased ICP 3. No component of the clinical triad of INPH 4. Symptoms are explained by other conditions		

A current method to predict the possible shunt effect is to investigate the CSF dynamics, preferably by a so called Spinal Tap Test which simulates shunting or by a Cerebrospinal Fluid Dynamic Test. A positive Spinal Tap Test result means that the patient shows significant clinical improvement when 40-50 ml of CSF are withdrawn (24). Transient improvement – hours and occasionally days – predict clinical improvement after shunt surgery. The CSF Dynamic Test registers the resistance against infusion of artificial CSF via lumbar puncture. These supplementary tests that gives physiological data could increase the prognostic accuracy to more than 90 % (12). However, a negative response to the test does not necessarily mean that the patient is unqualified for shunt treatment (25). Using these tests for selection of patients for shunt surgery would therefore result in exclusion of many patients who would benefit from the treatment.

Treatment

As previously stated, iNPH is underdiagnosed possibly due to the fact that symptoms and imaging findings can be confused with “normal aging” or mistaken as other neurological conditions, for instance Alzheimer´s disease (18, 19). iNPH is a reversible neurological disorder and one of few causes of treatable dementia. More than 80 % of the patients improve three months after neurosurgical treatment with peritoneal- or ventriculoatrial shunt which leads CSF from the ventricles to the peritoneal cavity (26). If contraindications for intraventricular shunts occur, a lumboperitoneal shunt can be used. A ventriculopleural shunt is considered when no other options remain.

iNPH is undertreated probably due to the difficulties in estimating benefits of the surgical procedure in relation to the risks (27, 28). Comorbidity, coagulation and immune status, age and clinical performance may influence the benefit-to-risk ratio negatively. The percentage of improved patients at three months and one year has since 2006 increased to more than 80 % and mortality rate have decreased to 0.2 %. Long-term effects are favorable with more than 70 % improved patients after five years in later studies (29). These results may be a consequence of improved hospital care as well as rehabilitation. Furthermore, the benefit-to-risk analysis and developed use of supplementary tests might have commenced better selection of patients (2).

Among those who are candidates for surgery there are still no routine to know who will respond from shunt treatment. Therefore it is important to find better methods to identify responders and non-responders.

Aim

This study is part of a research project initiated in 2014. The overall purpose of the project is to identify MRI- and CSF markers that predict the shunt treatment effect of iNPH patients and to hopefully introduce these results in the clinical routine.

The primary aim of this study was to test the hypothesis that preoperative perfusion in the bilateral frontal periventricular white matter, measured with MRI, can predict the effect of shunt treatment in patients with iNPH. Specific research questions were; 1) Can preoperative perfusion identify shunt responders from non-responders?; 2) Is there a linear relationship between preoperative perfusion and outcome after shunt treatment?

The secondary aim was to investigate the associations between frontal periventricular perfusion changes and postoperative clinical improvement.

Material and Methods

The current study is a part of a larger collaboration project between Sahlgrenska University Hospital, Gothenburg University and Östersund Hosptial, Umeå University. It is a prospective, blinded observation study including 152 patients diagnosed with iNPH according to American-European guidelines (20, 30) during the period 140101-160630 and subjected to shunt surgery. Diagnosis was based on clinical symptoms, physiological data and characteristic MRI. If the outcome of shunt surgery was considered uncertain preoperatively, often due to indistinct or atypical symptomatology, the CSF tap test (31) was used as supplementary test to support the indication for shunt surgery. Only those patients presenting a positive tap test were subjected to surgery. A lumbar puncture was performed preoperatively and all patients had a normal ICP (< 18 mm Hg).

All patients underwent a pre- and four-month postoperative investigation. Symptoms and signs were scored on the iNPH scale (21) at the NPH center of Sahlgrenska University Hostpital by an experienced neurologist, neuropsychologist and physiotherapist. Performance was evaluated in the four domains of gait, balance, neuropsychology and continence resulting in a total score from 0 to 100, where 100 represents normal performance and 0 maximal symptom burden, both pre- and four-month postoperatively. Participants were classified into shunt responders and non-responders based on an arbitrary chosen limit on the iNPH scale representing a clear clinical improvement (21). Improvement was defined as an increase of ≥5 points of

the total score (responders) and <5 points of the total score was defined as poor outcome (non-responders). The improvement corresponded to an increase in the domains - 12.5 points in the gait domain or 25 points in one of the remaining domains balance, continence and neuropsychology.

All patients received a ventriculo-peritoneal shunt with a Strata™ Valve (Medtronic PS Medical, Santa Barbara, USA) and an anti-siphon device. All shunts were working at the four-month postoperative evaluation.

Clinical aspects

In this study, 101 of the 152 patients were primarily included due to time limitation of the project. Furthermore, 77 patients were excluded as shown in figure 3.

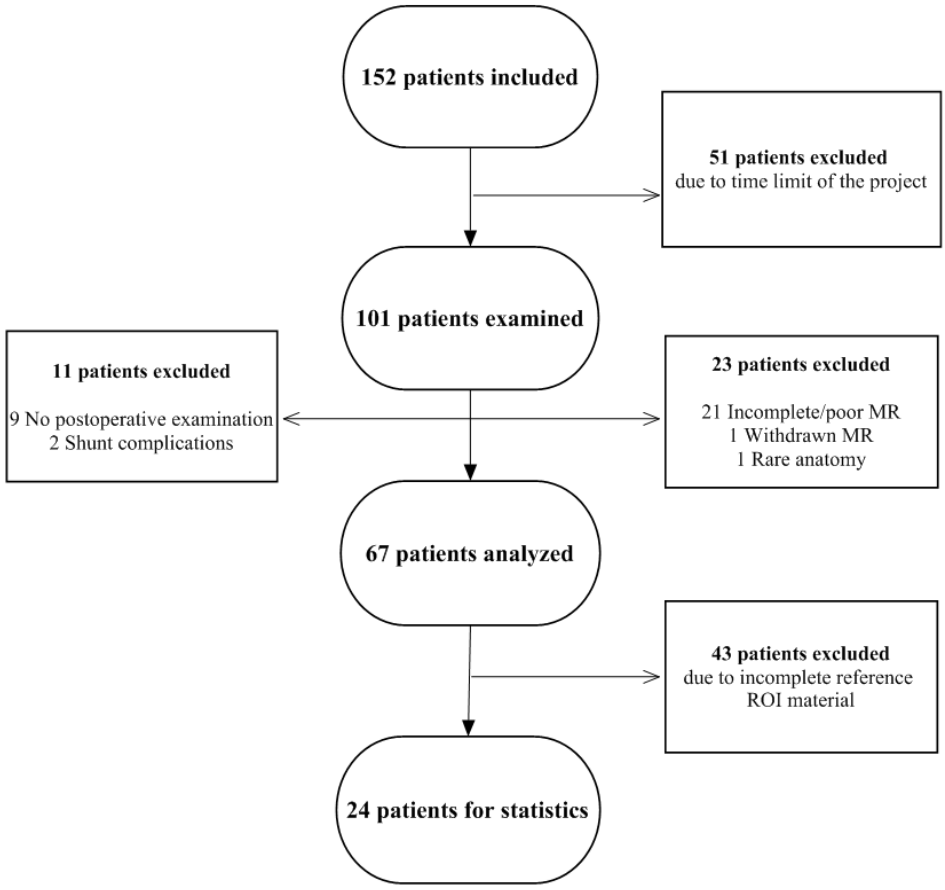

Figure 3. *Flow Chart on number of patients excluded in the current study*.

Thus, 24 patients, 20 male (83 %) and 4 female (17 %), median age at operation 76 years ranging from 58-91 years was further analyzed. Median disease duration was 24 months. Diabetes, hypertension and/or cardiovascular disease was present in 16 patients (67 %). Clinical demographics are summarized in table 2.

Table 2. *Demographic data of the studied group.*

	Demographic data
	N = 24
Age at operation (median, range)	76, 58-91
Sex (Male/Female)	20/4
Sickness duration in months (median, IQR)	24, 12-60
Comorbidity: CVD, hypertension or diabetes (yes/no)	16/8

IQR = interquartile range; Comorbidity = at least one of described conditions; CVD = cardio vascular disease.

Imaging

The brain was imaged pre– and four months postoperatively with a 1.5T Gyroscan Intera 9.1 system (Philips Medical Systems, Best, The Netherlands) using an eight-channel sense head coil. The morphological scan protocol included a transverse fluid-attenuated inversion-recovery (FLAIR) sequence (TE 100 milliseconds, TR 9000 milliseconds, IR delay 2500 milliseconds, slice thickness 3 millimeter, no slice gap, 48 slices, FOV 230 millimeter, image acquisition matrix 192×145 reconstructed to 256×256) covering the entire brain. DSC MRI perfusion images were obtained each 1000 milliseconds with a segmented k-space gradient-echo echo planar imaging (EPI) technique (TE 30 milliseconds, TR 500 milliseconds, flip angle 40^{o} , slice thickness 6 millimeter, no slice gap, 18 slices, FOV 230 millimeter, matrix 128 x 64, parallel imaging: SENSE factor 2). Using a power injector, a rapid bolus (5

milliliter/second) of 0.1 millimolar/kilogram body weight gadoterate meglumine (279.3 milligram/milliliter, Dotarem, Gothia Medical) was initiated at the 10th acquisition and administered through a 20–gauge IV line into the right antecubital vein, followed by a saline flush.

Data review

Clinical patient data were manually registered and introduced into a research database. Preparation of protocol for the analysis of perfusion in regions of interest (ROI) were made in several steps. The MRI studies were visually examined with regard to movement artifact, the ventricle shunt position, extent of the associated metal artifacts and the overall quality of the investigation. Thereafter the MRI surveys were registered and cataloged in the database based on quality and suitability for further image analysis. The material was unidentified and encoded according to a study code. Basic image processing was performed with window setting according to standard in-house protocols and documentation of selected windows. The data were manually registered and introduced into the research database.

Regions of interest

An anatomical region that has been shown to be engaged in NPH (10, 32, 33) determined the choice of ROI in this study – the anterior periventricular white matter – and reference ROI were drawn in the cerebellum to maintain a normalized relative CBF value.

The anterior periventricular white matter ROIs were drawn bilaterally, three to five millimeter wide, depicting the anterior horns of the lateral ventricles (usually in four

to five slices). The medial border of the anterior cap-like ROI was the lateral border of the cingulate sulcus and its lateral/dorsal border the head of the caudate nucleus.

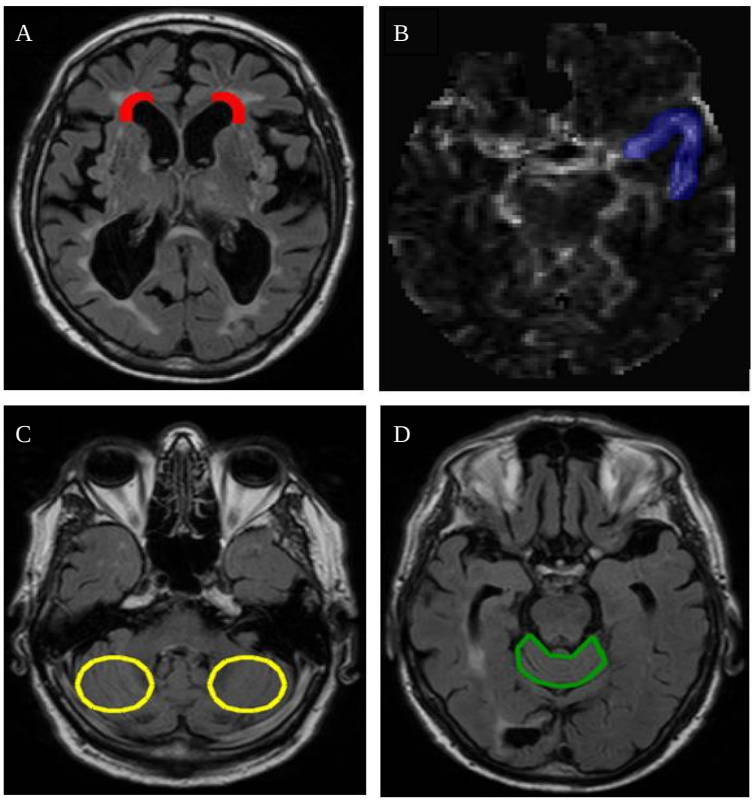

Figure 4. *Description of Region of interest (ROI) placement: A) Anterior periventricular white matter, dexter and sinister; B) Arterial Input Function (AIF) - necessary for perfusion parameter extraction; C) Reference in cerebellum - hemispheres; D) Reference in cerebellum – vermis.*

The cella media represented the cranial border. The anterior periventricular ROIs were positioned in the same manner regardless of the macroscopically appearance of the white matter in this region, as it has been shown that periventricular and deep white matter heterogeneities are similar in patients with NPH and Binswanger disease (BD) (11). In preoperative data, the mean perfusion value of the right and left ROI was used as the preoperative perfusion in further analysis (see below). Due to the right sided shunt artefact postoperative perfusion could not be obtained in the right periventricular region. Hence, the perfusion value of the left ROI was used for

assessing postoperative perfusion and compared with the left preoperative ROI when assessing postoperative perfusion changes.

The reference ROI in cerebellum, round and approximately three centimeters in diameter, were positioned in three adjacent slices centrally in each cerebellar hemisphere, covering both grey and white matter structures. Due to limited perfusion data in some patients, another reference ROI were manually drawn around the vermis area, in approximately three slices, if a reference ROI in each hemispheres could not be achieved.

Arterial input function (AIF) necessary for perfusion parameter extraction was drawn along the middle and distal part of the middle cerebral artery segment one (M1) and along the proximal middle cerebral artery segment two (M2). The artery was followed in two succeeding sections in the left hemisphere.

Post processing

Voxels within each ROI were averaged at each time point to form one signal time curve for every ROI. This curve was analyzed with an algorithm in the intent to quantify the perfusion. The mathematical process requires an "arterial input function" (AIF), which represents a dynamic time curve of the contrast agent injection into the ROI.

AIF selection

By tradition, the choice of AIF is manually performed and voxels that have a steep, narrow and high concentration-to-time curve are selected. This requires time and

since there are many voxels for the operator to choose from, different operators may not select voxels in the exact same way. Even the same operator may choose diverse AIF on the same dataset on two different occasions. Therefore it is suitable to use automatic or semi-automatic methods that select the most suitable voxels according to these criteria.

An in-house-developed and semiautomatic algorithm based on Mouridsen (34) was used to extract the AIF. The operator specifies a ROI that includes the artery of interest and the algorithm extracts an AIF from the subset of voxels within the ROI. This differs from the method described by Mouridsen where the algorithm selects voxels from the entire brain (34).

Deconvolution and normalization

As previously stated, the tissue residue curve which can be used to extract the perfusion parameters is found by de-convolving the measured data with the AIF. For this procedure we used an in-house-developed Fourier deconvolution algorithm (35). The deconvolution results in a tissue residue function in which the CBF can be extracted.

In order to compare perfusion across subsets the perfusion values were normalized to perfusion estimates of a reference ROI. The CBF estimate of the ROI in the anterior periventricular white matter was divided by the CBF value of the internal reference ROI in the cerebellum creating a relative CBF value (rCBF). Preoperative perfusion data were available in all 24 patients; both pre- and postoperative perfusion data in six.

Statistics

Since data were not normally distributed, nonparametric tests were used. To analyze changes over time (paired data), Wilcoxon´s signed ranks test for related samples was used. The Spearman rank correlation test was used to explore correlations. Mann Whitney U test was used to assess differences between independent groups. All significance tests were two-tailed and $P < 0.05$ was set as significant. All analyses were performed with IBM SPSS 24.0 for Windows.

Ethics

The study is approved by the Research Ethics Committee and all included patients or closest relatives have given written consent to participation.

Results

Clinical performance

Clinical performance improved after shunt treatment (p=0.000094). The median preoperative iNPH score was 54 ± 33 (Interquartile range, IQR) with a range between 34-81 points. Median postoperative improvement was 10 ± 15 (IQR) with a range between -9-39 points (p<0.001). Clinical characteristics of the 18 (75 %) improved and six non-improved patients are summarized in table 3.

Table 3. *Demographic data and clinical outcome of improved and non-improved patients.*

	Improved	Non-improved
	N = 18	N = 6
Age at operation (median, IQR)	76, 80-70	71, 78-67
Sex (Male/Female)	14/4	6/0
Sickness duration in months (median, IQR)	36, 63-12	16, 23-9
Comorbidity: CVD, hypertension or diabetes (yes/no)	10/8	6/0
iNPH score (median, IQR, range)	52, 41-72, 34-80	65, 49-78, 34-81
PiNPH score (median, IQR, range)	71, 61-84, 42-95	60, 40-80, 29-81

IQR = interquartile range; Comorbidity = at least one of described conditions; CVD = cardio vascular disease; iNPH score = preoperative clinical performance measured by the NPH scale (21); PiNPH = postoperative clinical performance measured by the NPH scale (21).

Associations between frontal periventricular CBF and clinical symptoms and outcome after shunt treatment

The median preoperative rCBF (n=24) was 0.4 (mL/100g/min, range 0.2-0.6). In the six patients with available postoperative perfusion data, the median rCBF increase was 0.09 (mL/100g/min).

The preoperative rCBF did not correlate with the preoperative iNPH scale score (r_s=-0.04, p=0.85). There was no correlation found between the preoperative rCBF and postoperative improvement on the iNPH scale visualized in figure 5 (r_s=0.06, p=0.77). Preoperative rCBF did not differ between improved or unimproved patients (p=0.97) viewed in figure 6. The rCBF improved after shunt treatment (p=0.03). The postoperative increase in rCBF is plotted against postoperative clinical improvement in figure 7 but did not show a significant correlation (r_s=0.60, p=0.21).

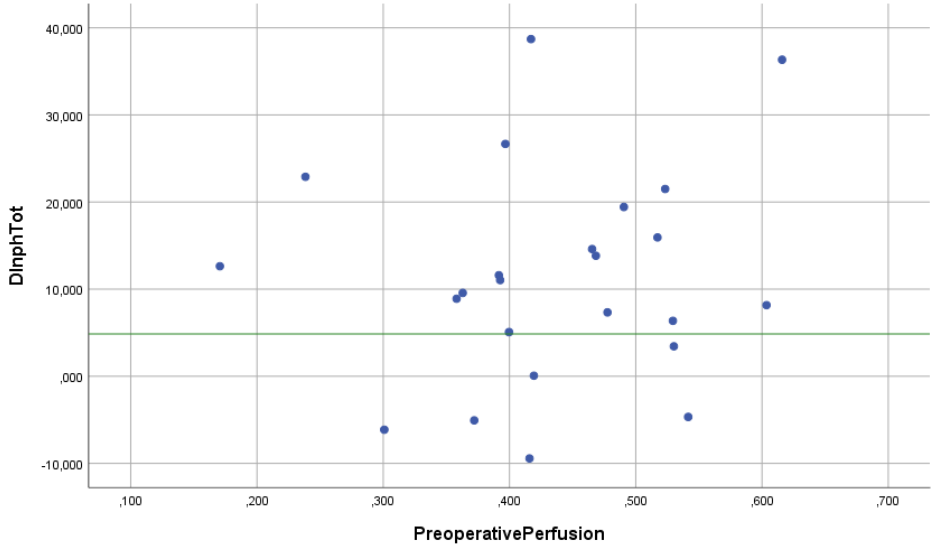

Figure 5. *Preoperative rCBF (PreoperativePerfusion) in relation to clinical outcome on the NPH scale (n=24). Green line represents cutoff value for clinical improvement.*

DInphTot = clinical improvement measured by the NPH scale (21).

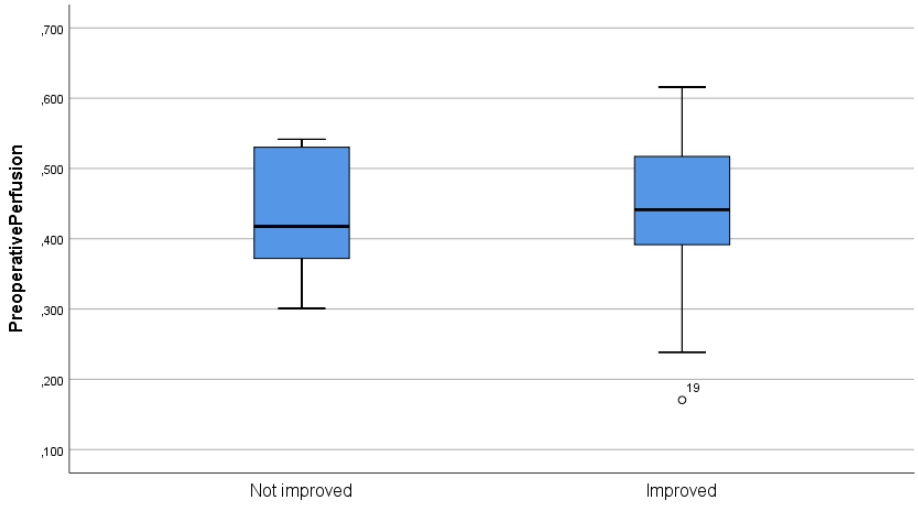

Figure 6. *Preoperative rCBF (PreoperativePerfusion) in clinically not improved (n=6) and improved (n=18).*

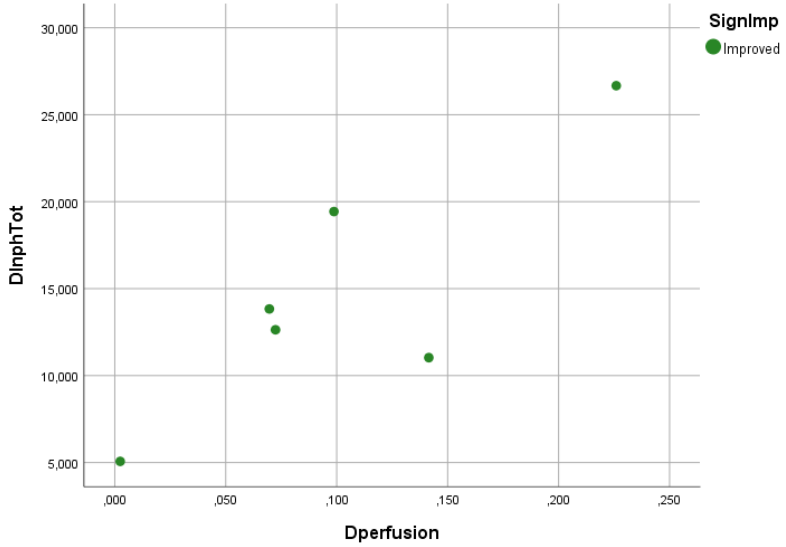

Figure 7. *Postoperative increase in rCBF in relation to clinical improvement (n=6).*

DInphTot = clinical improvement in points measured on the NPH scale (21); DPerfusion = rCBF improvement after shunt surgery measured by MRI perfusion.

Influence of vascular comorbidity on perfusion and clinical improvement

Patients with vascular comorbidity did not have significantly different preoperative rCBF compared to those without (p=0.23) visualized in figure 8. Patients with vascular comorbidity had a worse clinical outcome (median 7.8, IQR 15.9) than those without (median 17.7, IQR 23.3) (p=0.021).

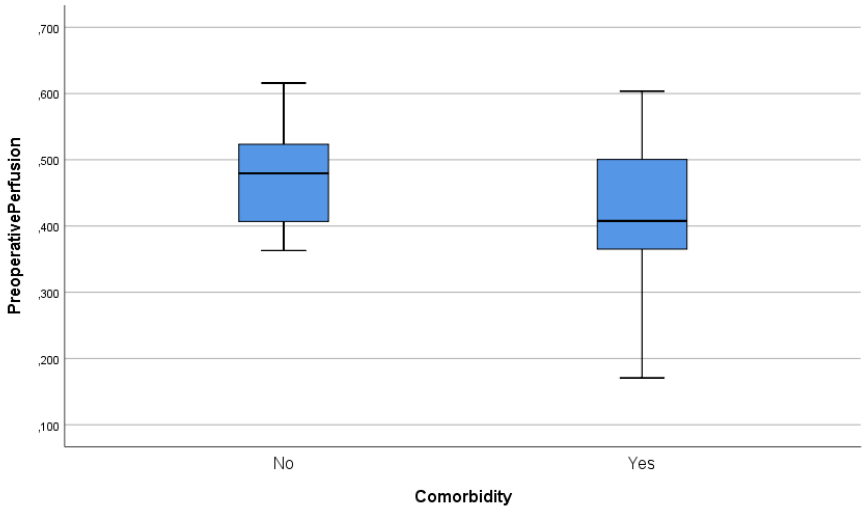

Figure 8. *Preoperative rCBF (PreoperativePerfusion) in participants with (n=16) or without (n=8) comorbidity.*

Discussion

Description of the study and Main findings

This prospective, observational study including 24 patients provides comprehensive data on preoperative clinical presentation, clinical outcome after shunt treatment, comorbidity and preoperative perfusion. Our primary aim was to investigate whether MRI perfusion imaging of the brain can predict the effect of shunt treatment in patients with iNPH. All participants were evaluated pre- and postoperatively regarding clinical performance and preoperative perfusion in a region of interest – anterior periventricular white matter. Eighteen patients (75 %) improved clinically (≥ 5 point on the iNPH scale) whereas six patients (25 %) did not improve (< 5 point on the iNPH scale) after shunt treatment. No correlation could be found between preoperative perfusion and preoperative performance or postoperative clinical improvement. The periventricular perfusion increased postoperatively in the six patients where postoperative perfusion could be assessed.

Clinical aspects

The study population (n = 24) were diagnosed with iNPH according to European-American guidelines (20). Clinical data were consecutively collected, converted to continuous data. The minor group size and the selection of individuals to which the iNPH disease contributes resulted in not normally distributed data. Participants were classified into improved and not improved based on an arbitrary chosen limit on the iNPH scale (21). The distribution of outcome rates, i.e. 75% responders (n=18) and 25% non-responders (n=6), is within the expected range (29), which indicates that the chosen limit is consistent with the limits of other, previously used scales.

Interestingly, the median duration of symptoms was shorter and the preoperative clinical performance better in the non-responder group compared with the responders group. Responders were also slightly older than non-responders. The inverse relationship is expected considering that iNPH is a progressive disease. However, the distribution of these clinical variables might be explained by a combination of the small size of the non-responder group and the large inter-individual variability of the natural course of iNPH (36).

Perfusion data

To evaluate the perfusion, ROIs were drawn in anatomical regions that previous studies have proposed to be engaged in NPH (10, 32, 33). In this project we studied the anterior periventricular white matter and a reference ROI were drawn in cerebellum to maintain a relative perfusion value for normalization.
A majority of the cerebellar perfusion data were limited and could not correlate with the processed FLAIR imaging data in which the ROIs were drawn. This resulted in limited data to analyze which explain the extent of excluded patients.

Preoperative perfusion was calculated as a mean value based on bilateral data from both right and left hemisphere. Postoperative perfusion analysis was limited due to shunt artifact in the right hemisphere. Hence, unilateral postoperative data assessed from the left hemisphere was analyzed but since bilateral perfusion changes are expected, this was not considered as a limitation. In spite of the small sample size and limitations described above, we believe that perfusion estimates are valid and representable.

Major results

In agreement with previous studies (12) postoperative clinical performance was significantly improved compared to preoperative clinical performance. No correlation was found between preoperative perfusion and preoperative clinical performance. In contrast with previous studies (37) the preoperative perfusion did not correlate with the clinical improvement. Preoperative perfusion could not be used to differentiate between improved and non-improved patients. These results may be explained by, apart from the small sample size. However, other factors related to the iNPH state may affect the clinical outcome, e.g. biochemical changes in the periventricular white matter. It is possible that the combined use of MR perfusion and CSF biomarkers may prove a better tool to predict reversibility (38).

A significant result was found comparing the pre- and postoperative perfusion. This corroborates with previous findings (37, 39) and confirms that this region is involved in the pathophysiology. Despite small sample we believe these results are valid. The increase of postoperative perfusion and the clinical improvement after shunt treatment did not correlate at a significant level. However, the Spearman correlation coefficient was 0.6 and the plot (figure 7) may indicate a linear relationship. This is in line with previous studies where a reversed condition in iNPH patients correlates with an improved perfusion (33, 40). Our result may be explained, as mentioned above, by the minor sample size. Larger sample sizes are needed to increase the power of these investigations.

Surprisingly, patients with vascular comorbidity had a worse clinical outcome compared to those without. However, previous studies have shown that the presence of cerebrovascular risk factors do not predict negative shunt treatment outcome (41).

Main limitations

There are several important limitations that should be considered and discussed. One main limitation is that the current study consisted of a small sample size because of inadequate MRI surveys and limited cerebellar perfusion data. This may cause falsely negative results due to lack of statistical power. Differences in gender distribution should also be recognized, nevertheless, we believe that our results are valid. Another limitation is that the ROI-analysis are to some degree operator dependent and in this study only one operator placed all ROIs which may affect the intra-observer reliability.

Furthermore, our study indicate a possible association between vascular comorbidity and outcome after surgery. Again, the small sample size may lead to incorrect significant associations. Further prospective studies are required to confirm the effects of perfusion as a predictor of treatment outcome.

The choice of cerebellum as an internal reference instead of the occipital cortex, used in previous studies (2), were done considering future clinical implementation. A ROI in cerebellum is easily prepared whereas the occipital ROI is much more complicated to perform. However, the limited cerebellar perfusion data restricted the possibility to evaluate cerebellum as a reference ROI. Nevertheless, perfusion values based on

available reference material were observed to be as expected along with perfusion improvement.

Main strengths

The main strengths of this thesis is the well examined and well diagnosed patients. Participants were consecutively collected and the clinical data are reliable, collected at one center and inter-professionally performed by a neuropsychologist, a physiotherapist and a neurologist. As previously stated, only one operator placed all ROIs which may not only be a limitation but also a strength due to the fact that collected ROI data might be similar and therefore more likely comparable. Furthermore, the process which extracted the perfusion parameters from the measured data was a valid and earlier published method (42).

Scientific and clinical value

This study evaluated the utility of perfusion in the anterior periventricular white matter for prediction of prognosis after shunt treatment in iNPH patients. However, our study could not show predictive perfusion measurement in the selection of shunt candidates shared with other adjunctive tests and do not exceed what can be accomplished by an interdisciplinary expert team. Further studies are warranted and larger sample sizes of both responders and especially non-responders are needed to increase the power of these investigations.

Conclusion

In this study, preoperative perfusion did not correlate with preoperative clinical performance or clinical improvement. This indicates that preoperative perfusion could not identify shunt responders from non-responders in patients with iNPH. However, a

significant result was found comparing the pre- and postoperative perfusion with a possible association to clinical improvement. Interestingly, presence of vascular comorbidity was associated with a poor clinical outcome.

Populärvetenskaplig sammanfattning

Användning av MR perfusion för att prediktera behandlingseffekt hos patienter med idiopatisk normaltryckshydrocephalus

Bakgrund

Idiopatisk normaltryckshydrocefalus (iNPH) är en neurologisk sjukdom karakteriserad av gång- och balanssvårigheter, nedsättning av intellektuella funktioner och vattenkastningsbesvär samt kommunicerande vidgning av hjärnans hålrum (ventriklar) och normalt intrakraniellt tryck. Diagnostiken baseras på en kombination av typiska symptom, karakteristiska fynd på CT eller MR av hjärnan och ryggvätskeundersökning. Tillståndet behandlas med en ventrikuloperitoneal- eller ventrikuloatrial likvorshunt vilket leder till förbättring hos ca 80 %. Trots goda behandlingsresultat med neurokirurgisk operation finns ännu inga tydliga objektiva metoder för att säkert förutspå behandlingseffekt och behovet av sådana metoder är stort.

Aktuell studie

Den primära målsättningen för vår aktuella studie var att utforska hypotesen om avbildning av blodflödet i hjärnan, mätt med DSC MRI, kan prediktera effekten av en shuntoperation hos patienter med iNPH. Detta är av medicinsk relevans då iNPH är ett behandlingsbart tillstånd och en av få orsaker till behandlingsbar demens samt att man vill motverka att patienter som inte får goda behandlingsresultat av shunt inte ska genomgå operation med tanke på de risker detta medför.

Inklusionskriterier för studien var patienter som efter utredning erhållit diagnosen iNPH enligt internationella riktlinjer samt erbjudits och tackat ja till operation.

152 patienter inkluderades under perioden 2014-01-13 – 2016-06-30. Klinisk undersökning med kvantifiering av symtom, MR hjärna samt ryggvätskeundersökning utfördes före och fyra månader efter operation.

Anatomiska regioner i hjärnan med påverkat blodflöde som i tidigare studier visat sig vara engagerade vid iNPH var avgörande för val av region av intresse (ROI). I denna studie tittade vi framför allt på anterior periventrikulär vit substans med referens från vävnad i lillhjärnan.

Studien är godkänd av forskningsetisk kommitté och alla inkluderade patienter har lämnat skriftligt samtycke till deltagande.

Resultat

24 patienter studerades med avseende på klinisk förbättring och blodflöde i specifika regioner i hjärnan. 18 patienter (75 %) förbättrades kliniskt medan sex patienter (25 %) inte förbättrades kliniskt efter shuntoperation.

Studien kunde inte visa på någon korrelation varken mellan blodflöde i anterior periventrikulär vit substans före operation och klinisk prestation före operation eller mellan blodflöde före operation och klinisk förbättring efter operation. Studien fann däremot ett signifikant resultat vid jämförelse mellan förbättring av blodflöde i samma område före och efter operation ($p=0.03$). Oväntade resultat visade också att komorbiditet påverkar kliniskt förbättring, vilket motsäger tidigare studier.

Diskussion och konklusion

Studien kunde inte påvisa ett prediktivt värde av blodflödet i anterior periventrikulär vit substans. Studieresultaten styrker i viss mån vår hypotes om att förändrat blodflöde i denna del av hjärnan är kopplat till centrala sjukdomsmekanismer samt eventuellt kan prediktera effekten av en shuntoperation hos patienter med iNPH. Då studien baseras på en liten studiepopulation kan resultaten vara missvisande på grund av låg statistisk styrka. Större studiepopulationer av både respondenter och framför allt icke-respondenter behövs för att öka styrkan av dessa undersökningar.

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