

Quantitative Motor Examination in Normal Pressure Hydrocephalus Patients

Robert McGovern, Doris Duke Clinical Research Fellow

1. STUDY PURPOSE AND RATIONALE

1.1 Purpose

Normal pressure hydrocephalus (NPH) is a neurologic disorder that causes three groups of progressive symptoms that are very disabling: gait and balance problems leading to falls, urinary incontinence, and dementia. This condition is in urgent need of clarification, because while the diagnosis of NPH is very difficult to make with confidence, the gait and postural instability caused by NPH can respond to neurosurgical treatment. The purpose of the present project is to develop methods to improve our ability to diagnose NPH and predict patients' response to neurosurgical treatment.

1.2 Background

1.2.A Clinical Features of NPH

NPH is a neurologic disorder that affects the elderly and causes, in variable order of onset, a triad of gait and balance difficulties, urinary incontinence, and dementia. The motor symptoms overlap with symptoms that can be caused by Parkinson's disease (PD), and the major diagnostic difficulty is usually in distinguishing between these two conditions. The major effects of NPH on gait and balance include slowing of gait, shortening and shuffling of stride, and postural instability. This last symptom is a manifestation of poor postural reflexes: the person can usually stand without difficulty, but any amount of jostling or tilting can result in falling, because the normal "righting" responses are impaired. As the disease advances, postural instability becomes severe enough that the person cannot even stand without assistance. There is a characteristic "retropulsion", consisting of backward tilting of the trunk when standing, which leads to a tendency to falling backwards. Along with slowing and shortening of stride, many patients develop difficulty initiating gait at all (a type of "motor freezing", or "motor block"), which leads to a characteristic "magnetic" appearance to the gait: it is as if the person's feet are stuck to the ground and are difficult to lift off the ground.

Rates of prevalence of NPH are difficult to obtain because there is no reliable method for confirming the diagnosis. Previous epidemiological studies suggested that NPH was a rare disorder with estimates in the range of 1.3-2.2/1,000,000 inhabitants[1], 0.4% of the population aged 65 and older[2], and 1.6% of all dementias[3]. There has been a more recent effort to better categorize the prevalence and incidence of NPH and these estimates indicate that NPH is more frequent than previously thought. Current studies show an overall prevalence of 1.8-21.9/100,000 inhabitants[4, 5], 2.9% of the population aged 65 and older[6] and 5.4% of all dementias[7]. Gait difficulties and falls are the main presenting symptoms of NPH[8-10], and are a major cause of morbidity in the elderly[11, 12].

The major finding on imaging studies is hydrocephalus, that is, enlargement of the ventricles of the brain, which is visible on head CT scans as well as brain MRI. Because all the ventricles are enlarged, the hydrocephalus is of a "communicating" type, i.e., not due to an identifiable obstruction in the flow of cerebrospinal fluid (CSF). Unlike other forms of hydrocephalus, CSF pressure is normal when measured by performing a lumbar puncture. This finding makes the pathophysiology of NPH mysterious, because it is not clear how the ventricles become enlarged without a concomitant increase in CSF pressure. Several theories have been proposed, with various degrees of experimental support[13-16].

1.2.B Diagnosis of NPH

A diagnosis of NPH is usually suspected when a person experiences gait difficulties of a parkinsonian type (short shuffling stride, slow gait, postural instability) along with hydrocephalus. The suspicion is enhanced by the presence of memory problems or urinary incontinence, and if the gait difficulties are accompanied by a "retropulsed", rather than stooped posture, and by difficulty initiating gait.

However, beyond the clinical suspicion raised by these signs, there is no method for reliably making a diagnosis of NPH. Various clinical and imaging tests have been proposed to distinguish NPH from other forms of parkinsonism and dementia. These criteria include the presence of parkinsonian signs in the upper body, the amount of generalized atrophy in proportion to the severity of hydrocephalus, and various specialized imaging studies that measure rate of CSF flow through the ventricles[17-20]. These criteria have invariably failed to generate a clear discrimination between NPH and other conditions.

A major difficulty in establishing criteria for the diagnosis of NPH stems from the fact that this condition is not associated with any specific neuropathology. Therefore only clinical criteria can be used.

The common current approach to the evaluation of NPH is to assess a patient's clinical response to the temporary removal of CSF. The traditional method, or "tap test," has been to admit the patient to the hospital, perform 3 large-volume lumbar punctures, on each of 3 consecutive days, and to compare clinical examination before and after CSF removal. A more modern approach is to place a lumbar drain that allows continuous CSF drainage for three days, and compare clinical examinations before and after the three days of drainage.

The effect of temporary CSF removal is used to predict whether the patient would benefit from permanent reduction of CSF volume, which is then accomplished through the placement of a ventriculoperitoneal (VP) shunt. The predictive value of these tests is unfortunately limited. The "tap test" described above is thought to have good positive predictive value in the range of 73-100% but poor negative predictive values ranging from 23-42%[17]. In addition, the tap test is neither particularly sensitive nor specific, with sensitivities reported between 26-62% and specificities from 33-100%[17]. Placing a lumbar drain increases the sensitivity of NPH diagnosis with predictive values in the same range as the tap test[17].

1.2.C Treatment of NPH

Placement of a VP shunt produces variable amounts of improvement. Most of the outcome data in NPH patients come from retrospective studies using many different outcome variables. Nevertheless, the vast majority of studies show clear benefits in areas of motor function (gait and postural stability) for 60-75% of patients[10, 21]. However, due to this variability in outcome measures and the lack of blinded, controlled studies, there has not been clear evidence of improvement in either cognitive function or urinary incontinence after VP shunt. Multiple studies have shown either benefit[22-26] or no benefit[27-30] in cognitive functioning after VP shunt placement.

1.3 Rationale

Because VP shunt placement can be dramatically effective in relieving gait and balance problems in NPH, at least for certain patients, and because these symptoms cause considerable morbidity, there is strong interest in improving our ability to identify which patients will benefit from this procedure. At this point the decision to proceed to neurosurgical treatment can only be made with noisy information: the predictive value of clinical assessments and response to temporary CSF removal are too low (as mentioned above in Section 1.2.B) to unconditionally determine treatment decisions.

We hypothesize that some of the variability affecting the clinical assessment of NPH stems from the lack of objective measures in current clinical assessments. This leads to variability in assessment techniques and variability in the data used to make a treatment decision. For example, the pull test is performed with variable intensity depending on the person performing the test, who may be gentler with some patients than with others based on other clinical signs. Indeed, it has been recognized that there is great variability in pull test techniques[31], which makes the test unreliable as currently performed.

We propose to address the problem of variability in the clinical assessment of NPH by developing objective, quantitative, computer-based measures of clinical status relevant to treatment decisions for this condition. Unlike previous studies, which have focused on single measures[32, 33], we plan to develop quantitative versions of all three major motor domains affected by NPH: speed of limb movements, gait, and postural reflexes. Moreover, we plan to capitalize on the knowledge accumulated from clinical experience: rather than devise new quantitative tests for NPH, we will quantitate the existing clinical tests. The essence of our proposed approach will be to use an infrared motion capture system to record the clinical motor tests that are normally performed by movement disorder neurologists for evaluating NPH. The resulting motion data will then be available for objective analysis of clinical findings.

2. STUDY DESIGN AND STATISTICAL PROCEDURES

2.1 Rationale for Study Design

Our main goal will be to reduce the variability associated with the clinical evaluation of NPH. Our approach will be to reduce variability in the clinical evaluation by quantitatively measuring selected portions of the neurologic examination using a computerized motion-capture system.

2.2 Approach

2.2.A Current Clinical Practice

In practice, when a patient is suspected of having NPH, the following procedure is commonly followed at Columbia University Medical Center (CUMC). First, a full clinical evaluation is performed by a movement disorders specialist (in the Division of Movement Disorders, Dept. of Neurology). Besides a detailed clinical history and neurologic examination, this evaluation includes: 1) a brief cognitive assessment using the MoCA rating scale (Montreal Cognitive Assessment[34]); 2) a videotaped assessment of motor, gait, and postural stability function according to the Unified Parkinson's Disease Rating Scale (UPDRS)[35] and the "timed-up-and-go" test[36]. The UPDRS includes a set of motor examination tests designed to assess the presence of parkinsonism in various body parts. There are 14 items in the motor component of the UPDRS, and each is scored by the examiner on a severity scale from 0 (no deficit) to 4. It includes tests of motor speed (repeatedly opening and closing hands, foot tapping), ability to arise from a chair and assessment of posture, features of gait (speed, stride length, arm swing, number of steps employed in turning), and the pull test, which is described below. Second, the patient is admitted to the hospital for 3-day drainage of CSF through a lumbar drain, which is placed and removed by a neurosurgeon. The videotaped assessment of motor, gait, and postural reflexes is performed on the day of admission, before placement of the lumbar drain, and on the day of discharge, after removal of the drain. Third, the neurologist and neurosurgeon review the videotaped examinations to decide whether there was a clinical improvement after CSF drainage. If this is the case, the patient is offered to have a VP shunt placed. If this is not the case, the patient is followed by the movement disorders neurologist and other treatment options are considered. For example, if the most likely alternative diagnosis is Parkinson's disease, then treatment with medications for Parkinson's disease is considered. An estimated 50 patients undergo NPH assessment at CUMC each year.

2.2.B Proposed Quantitative Recording

Patients who are being clinically evaluated for NPH at the *Center for Parkinson's Disease and Other Movement Disorders* at CUMC will be offered the opportunity to participate in the study. Their participation will consist of having their movements recorded by a portable motion-capture system while they undergo the standard neurologic examination for NPH as outlined above. This recording system is non-invasive: it requires only the placement, via paper tape, of small reflective lightweight plastic markers on various parts of their body (head, shoulder, elbow, wrist, hip, knee, and foot). They will be tested by the neurologist in the standard clinical tests for NPH. The components of the neurologic exam that are currently considered crucial in the assessment of NPH are mainly a subset of the UPDRS [35]. These are: rapid alternating movements of the hands and feet (items 23-26 of the UPDRS); ability to arise from a seated position (item 27); speed and stride-length of walking (item 29); number of steps required to turn in place and postural stability, as assessed by the pull test (item 30). Gait will be recorded by having patients walk on a computerized mat that records position and time of the steps. Patients will be tested before and after undergoing a lumbar drain trial. If they then also undergo neurosurgical placement of a VP shunt, their examination will be again quantitatively recorded before and after shunt placement. *The decision to place a VP shunt will be made according to current clinical practice and will not be influenced by results of our quantitative recording.* To ensure this, all clinicians who will be making decisions affecting patient care will be blinded to the results of the quantitative recording throughout the duration of the study. After collecting data from all subjects, we will then analyze the resulting data to establish the predictive value of our new quantitative measures, i.e., how well do these measures predict a patient's response to a VP shunt based on their response to a lumbar drain trial.

2.3 Data Collection

2.3.A Movement-recording systems

We will use two non-invasive movement measurement techniques to obtain quantitative movement measures during the neurologic examination. The first is a motion-capture system (Proreflex system) that we regularly use in our laboratory to record motion of the hand. The system consists of an infrared high-speed video camera (Proreflex, manufactured by Qualisys) that records the positions of reflective markers that are taped on the moving body part. The markers are small (2-cm diameter) lightweight plastic grey spheres. The camera records their infrared reflection and instantly computes the marker's x, y coordinates. Although this system is referred as a video-based system, it does not record video images, but rather only the positions of the markers attached to the subject. The camera will be controlled by a Macintosh laptop computer using custom-written software. For each component of the exam, the camera will record position data for several seconds at a sampling rate (100 Hz) that is high enough for subsequent calculation of speed and acceleration. The position data will be stored on the computer for offline analysis.

The Proreflex system is well-suited to record movements of the individual limb or of the entire body in 2 dimensions. We will use this system to record rapid movements of the hands and feet (UPDRS items 23-26), and to record the response to the pull test (item 30).

A limitation of our Proreflex system is that it is not well suited to record gait. For this purpose we will use a second measurement device, the Gait-Rite system. This system consists of a 12 foot-long mat embedded with sensors to record human footsteps. It has an electronic interface which sends to a laptop computer information about where and when each step landed. This data is stored for offline analysis. We will use it to record stride length, walking speed, and number of steps required to turn in place. The UPDRS lists these aspects of gait under one item (item 29), but we will be able to record them separately for more detailed analysis.

The examination will also be videotaped with a standard video camera in case it becomes necessary to review the experimental procedure at the time of offline analysis of movement data.

2.3.B Data To Be Collected

We will use non-invasive computerized motion-capture equipment to quantitatively record subjects' movement during the clinical examination. The quantitative data will be recorded as part of the neurologist's clinical examination. We will then perform offline analysis of the movement data to obtain objective measures of movement limitations. During this study, the clinical evaluation will proceed without any information about the objective measures being recorded.

The raw data will be position and time data for the following conditions.

Finger tapping: position of the index fingertip, thumb fingertip, and first and second metacarpophalangeal (MCP) joints

Foot tapping: position of the heel (posterior-most medial point on calcaneus), foot tip (medial aspect of great toe), and ankle (medial malleolus).

Pull test: position of the shoulder, elbow, wrist, hip, knee, ankle (lateral malleolus), heel, and foot tip.

Walking: position of each stride on a 12 foot stretch of hallway.

Turning: number of steps required to turn from facing one direction to facing the opposite direction.

2.3.C Conditions

Each patient will be tested in at least two of four possible conditions.

Pre-drainage condition. This refers to the initial testing, before placement of the lumbar CSF drain.

Post-drainage condition: on the day of discharge from the 3-day inpatient stay for CSF drainage. Testing will be performed within 1 hour after the drain has been removed.

Pre-shunt condition. For patients who proceed to have a VP shunt placed, testing will be repeated on the day of admission.

Post-shunt condition. For patients who underwent VP shunt placement, testing will be repeated after the shunt's settings have been adjusted to their optimal values, as chosen by the treating neurosurgeon. Usually this occurs within 1-3 months after the surgery.

2.3.D Data Processing: Calculation of Kinematic Measures

Position data obtained from each clinical examination will be processed as follows. For the Proreflex system, the raw data will be filtered at 6 Hz with a zero-lag low-pass Butterworth filter, in order to remove the small amount of high-frequency noise inherent in the recording system, and not reflecting actual movement. Then the following kinematic measures will be calculated using custom-written routines.

Finger-tapping. The distance between first MCP and fingertip for the forefinger will be used to assess finger length (which varies from subject to subject). The amplitude of the excursion of the thumb and forefinger will be first be normalized to the length of the forefinger, in order to remove the effect of inter-subject variations in finger length. Frequency and decrement of finger-tapping will be calculated from the position data. Frequency is defined as the number of finger taps in a 15 second time period. Decrement is defined as the difference in peak amplitudes during the first 5 seconds and the last 5 seconds of finger tapping.

Foot-tapping. Calculations equivalent to those used for finger-tapping will be employed for foot-tapping. Normalization will be based on foot length, measured as the distance from calcaneus to great toe.

Pull test. The pull test consists of applying a backward displacement to the trunk and measuring the patient's response, which is a step backwards taken to recover balance. One source of variability in this test stems from the trunk's flexibility: some patients arch their back in response to the pull, which effectively reduces the amount of the pull's destabilizing effect, because the body's center of mass (COM) is displaced less than if the trunk is kept rigid. Another source of variability is the strength of the pull test, which varies from examiner to examiner. Finally, for a given intensity of pulling, the actual backward displacement varies from patient to patient, due to variations in patients' height and weight, which constitute variations of inertial mass.

We will address these issues by using the raw data to calculate the length of the upper arm, forearm, trunk, thigh, and lower leg. These will be used for a "stick-limb" biomechanical model of the body [37], from which the body's center of mass (COM) will be calculated. The markers' positions will then be used to calculate the time course of the body's COM. The pull test is composed of two time periods: before and after the foot is first lifted. Movement of the COM before foot lift is due to the examiner's pull, and we will take this as the main dependent measure of the pull test. We will calculate peak and average backward acceleration of the COM before foot lift. This will be a measure of the pull's intensity. We will then measure the foot's step latency (i.e., when the foot was first lifted after the pull was applied), amplitude, and peak acceleration. These will be measures of the patient's response, i.e., measures of postural reflexes. Thus, to assess the patient's postural response, we will use a measure of step length normalized for a given COM acceleration (step length/COM acceleration).

Note: the camera will record position of the right arm and leg and right side of trunk. The examiner will ask the patient to react to the pull using the right foot first. This will ensure that the quantitative measures always relate to the subject's initial response, rather than a second step. Whether the patient is right- or left-footed will not matter, because comparisons before and after CSF drainage will be within-subject.

Walking. We will calculate stride length and frequency from the foot position data recorded from the Gait-Rite mat.

Turning. We will count the number of steps taken to turn in place by 180 degrees from the Gait-Rite foot position data. Using number of steps obviates the need to account for the patient's step width or for the patient's initial base stance (narrow vs. wide) since each patient needs to turn 180 degrees regardless.

2.4 Statistical Analysis

2.4.A Hypothesis testing methods

The study's design is to record kinematic measures from those patients who undergo VP shunting on four occasions, 1) before CSF drainage, 2) after CSF drainage 3) before VP shunt and 4) after VP shunt. We will test specific hypotheses for each kinematic measure as outlined below, but our main outcome measure for each measure will be a linear regression analysis designed to test whether specific kinematic measures or combinations of kinematic measures can predict VP shunt outcome.

Hypothesis for Kinematic Measure #1: Finger tapping

We will test the hypothesis that NPH patients will improve in both frequency and decrement of finger tapping (see below for definitions of terms) after VP shunting. The difference seen before and after drainage will be correlated with the difference before and after VP shunting. We will use simple linear

regression to detect if there is a linear correlation between an improvement in these measures after drainage and improvement after VP shunting. Though this would be an interesting result, we are also interested if our measures are related to clinical improvement in gait. To test this, we will compare the difference in our measures before and after drainage among patients who showed gait improvement (as defined below) and patients who did not show gait improvement. We can compare these group mean differences with an independent sample t-test. Finally, these measures will also be included in a multiple logistic regression model to test whether a combination of some or all of our kinematic measures can predict gait improvement.

Frequency is defined as the number of finger taps in a 15 second time period. Decrement of finger tapping is defined as a difference in the peak amplitude during the last 5 seconds from the first 5 seconds. Our clinical measure of gait improvement will be a binary outcome measure categorized as either “improved,” or “not improved” as judged by the principal investigator of this study (Dr. Pietro Mazzoni, a movement disorders specialist) and a co-investigator of this study (Dr. Guy McKhann, a neurosurgeon experienced in treating NPH patients with VP shunts) after optimization of shunt settings. This is in accordance with current clinical practice. It is again important to note that Drs. Mazzoni and McKhann will make these judgments without any knowledge of the quantitative recording results throughout the duration of this study.

Hypothesis for Kinematic Measure #2: Foot tapping

We will test the hypothesis that NPH patients will improve in both frequency and decrement of foot tapping before and after VP shunting. We will use the same regression analysis and t-test as described above in “finger tapping.” In this case, frequency is defined as the number of foot taps in a 15 second time period. Decrement of foot tapping is defined as a difference in the maximum angle during the last 5 seconds from the first 5 seconds.

Hypothesis for Kinematic Measure #3: Pull test

We will test the hypothesis that NPH patients will improve in step length/COM acceleration after VP shunting (see section 2.4.D for explanation of step length/COM acceleration). We will use the same regression analysis and t-test as described above.

Hypothesis for Kinematic Measure #4: Gait velocity

We will test the hypothesis that NPH patients will improve in gait velocity after VP shunting. We will use the same regression analysis and t-test as described above. Gait velocity is defined as distance traveled/time.

Hypothesis for Kinematic Measure #5: Turning in place

We will test the hypothesis that NPH patients will improve in the number of steps required to turn in place. We will use the same regression analysis and t-test as described above.

2.4.B Power analysis

The quantitative measures we propose to record are new, and thus there are no directly relevant existing studies to guide our selection of subject numbers. However, one large study used multiple logistic regression analysis to show that the decision to place a shunt based on clinical and CT findings combined would result in gait improvement 64% of the time. Thus, as potential improvements over typical clinical findings, but without the benefit of CT findings, we might expect the measures included in our multiple logistic regression model to explain 50% of the variability in outcome. This equates to a correlation coefficient (r) of ~ 0.7 . To detect an r of 0.7, we will need 14 subjects at the $\alpha=0.05$ level of significance with a power of 80%. In addition, previous studies of gait analysis in patients with NPH reported

standard deviation of various measures around 20% of recorded mean values for patient groups[33, 38]. We are interested in detecting a 20% difference between Pre-drain and Post-drain conditions in mean values of kinematic variables. In order to have 80% power to detect such a difference at the $\alpha = 0.05$ level, the sample size required is 17 patients in each group. We will plan to enroll 40 patients in order to account for potential attrition. The major possible sources of attrition that we can predict are scheduling problems and patients changing their minds at some point in the course of their treatment.

The number of patients admitted for CSF drainage trial at CUMC by the above physicians was approximately 50 in the last year. Therefore we do not expect to have any difficulty recruiting a sufficient number of patients for this study.

3. STUDY PROCEDURES

3.1 Facilities

Subject testing will be conducted in the *Center for Parkinson's Disease and Other Movement Disorders* in the Department of Neurology of CUMC. The *Center for Parkinson's Disease and Other Movement Disorders* provides diagnosis and treatment for patients with Parkinson's Disease, NPH and a variety of other movement disorders. Thus, patients with gait difficulties are normally seen here by movement disorder specialists, such as Dr. Pietro Mazzoni, the principal investigator of this study. If patients are offered and elect to undergo VP shunting, Dr. Guy McKhann, a neurosurgeon experienced in the placement of VP shunts and co-investigator of this study, will perform the VP shunt. Data analysis will occur in the *Motor Performance Laboratory* headed by Dr. Mazzoni and Dr. John Krakauer (a co-investigator of this study). It is a 600 sq. ft. facility located in the Neurological Institute on Columbia University's Health Sciences Campus.

3.2 Testing Procedure

The experimental procedures are designed to dovetail with the standard neurologic examination of NPH patients. These will be performed by Dr. Mazzoni, who regularly evaluates patients with movement disorders, including NPH, in the *Center for Parkinson's Disease and Other Movement Disorders*. Thus, the patient's experience will be similar to a normal clinical office visit, except for the additional time needed to learn about the study, provide informed consent, and have markers placed on the arms and legs for motion capture. We estimate this additional time at approximately 30 minutes. The evaluation will include quantitative recording of the neurologic examination. The clinical rooms on this floor have ample space to accommodate the equipment for quantitative movement recording during the neurologic examination. The patients will then be admitted to Milstein Hospital at CUMC for the CSF drainage trial. On the third day, repeat testing will be scheduled for within one hour after removal of the CSF drain. If the patient is offered and elects to undergo VP shunt placement, Dr. Mazzoni will perform the standard neurological evaluation which will again include quantitative recording on the day of VP shunt placement. Dr. Guy McKhann will then place the VP shunt. Again, it is important to note that Dr. McKhann will be blinded to the results of this study throughout its course so as not to affect the decision of whether or not to place the VP shunt. Subsequent quantitative recording will occur after VP shunt placement after Dr. McKhann has determined that the shunt settings are optimized and the patient is experiencing maximum clinical benefit. This occurs typically within 1-3 months after VP shunt placement.

4. STUDY DRUGS OR DEVICES

No drugs or devices will be tested as part of this study.

5. STUDY QUESTIONNAIRES

This study will not make use of questionnaires.

6. STUDY SUBJECTS

As outlined above, we will be studying patients suspected of having Normal Pressure Hydrocephalus.

6.1 Brief description of diseases studied in this project

Normal Pressure Hydrocephalus (NPH) is a neurologic disease classically presenting with the triad of gait problems, dementia and urinary incontinence along with hydrocephalus, or enlargement of the brain's ventricles, on CT. It is a disease of the elderly, mainly affecting individuals >65 years old. Many mechanisms have been proposed in order to try to explain the symptoms of NPH, but none have yet gained acceptance. Because hydrocephalus is a main feature of NPH, neurosurgeons have most commonly treated NPH by placing a tube from the ventricles into the abdominal cavity in order to drain excess cerebrospinal fluid (CSF) from the ventricles. This is termed ventriculoperitoneal (VP) shunting. Indeed, a significant proportion of patients (60-75%) can benefit from VP shunting, particularly in terms of their gait and balance problems. Improvements in cognitive and urinary function is more variable as some studies claim to show improvement in cognition and urinary function while others show none.

6.2 Patient Selection

We will obtain movement data from patients with suspected NPH who have been selected, during their clinical evaluation, for CSF drainage trial. The data will be collected as part of the neurologist's evaluation on the day of admission for the 3-day CSF drainage trial, and on the day of discharge. If the patient is offered and elects to undergo VP shunt placement, he/she will be offered the opportunity to again be quantitatively recorded during his/her neurologic exam before and after VP shunt placement.

6.2.A Subject Selection Criteria

Inclusion criteria

All patients suspected of having NPH and scheduled to have inpatient admission for CSF drainage trial at CUMC will be considered for possible participation in this study.

Exclusion criteria

Patients with dementia of sufficient severity to impair their ability to make health-care decisions for themselves will be excluded. This criterion will be based both on the referring physician's impression and on a Mini-Mental State Examination (MMSE; [39]). The MMSE will be performed as a back-up procedure, just before informed consent has been obtained. Patients who score between 18-23 are considered to be mildly cognitively impaired and <18 to be severely cognitively impaired[40]. Thus, if the MMSE score is < 23, the patient will be excluded from the study.

6.2.B Expected Subject Group Enrollment

Normal Pressure Hydrocephalus patients undergoing VP shunt. (n=20) It is expected that, as part of standard work-up and treatment of NPH, a substantial proportion of patients, after undergoing the CSF drainage trial, will be offered the option to have neurosurgery for VP shunt placement. *This decision will be made by the treating neurologist and neurosurgeon according to current clinical practice, independent of analysis of quantitative data.* Patients who choose to undergo VP shunt placement will also be offered the opportunity to have quantitative testing performed before and after the surgical procedure.

7. RECRUITMENT

All of our recruitment procedures will be in compliance with the latest HIPAA regulations on the conduct of research with human subjects. We will recruit patient subjects from the Center for Movement Disorders in Columbia University's Department of Neurology.

Patient subjects will include people suspected of having NPH. We expect a minority of patients will fail to improve after CSF drainage trial and may be subsequently diagnosed with other movement disorders, mainly Parkinson's Disease.

7.1 Recruitment Methods

Study patients will be recruited among patients suspected of having NPH and who are scheduled to undergo inpatient CSF drainage trials at CUMC. We will send a letter to physicians who regularly evaluate patients for NPH at CUMC, namely, the neurology attendings in the Division of Movement Disorders in the Dept. of Neurology (Drs. Stanley Fahn, Paul Greene, Blair Ford, Steven Frucht, Cheryl Waters, and Elan Louis), and to the two neurosurgical attendings who are experienced in the treatment of NPH patients in the Dept. of Neurological Surgery (Drs. Guy McKhann and Robert Goodman). The letter will describe the study and the inclusion and exclusion criteria, and will request names of patients who may be contacted to participate in this study.

Patients identified by their physicians as possible candidates for the study will be sent a letter describing the study, and will receive a follow-up phone call asking whether they are interested in learning more about the study. If they agree, they will be scheduled to arrive 30 minutes before the scheduled clinical evaluation so that they may be informed about the study, provide informed consent, and be prepared for quantitative movement recording.

7.2 Information given to Subjects

The Principal Investigator will personally obtain written informed consent from each subject. In this meeting he will summarize the purpose of the experiment and the methods involved. The principal Investigator will then temporarily leave the room and the subject will be allowed to read the consent form (see attached) for as long as he/she wants. Afterwards, the Principal Investigator will address any questions the subject might have about the consent form or about the experiment.

8. CONFIDENTIALITY OF STUDY DATA

Every subject tested in the lab will be assigned a random code that will be used to uniquely identify the subject throughout the experiment. The subject's name, code, and demographic information will appear only in a single document maintained on a secure computer under password protection in the lab. All other computer files and data related to each subject will use only the numeric identifier. The data emerging from analysis of movements is a set of numeric variables derived from complex calculations, including differentiation and filtering. In our experience, this processed data is so removed from what the experimenter observes during testing sessions, that it is not possible to identify individual subjects from the analyzed data.

The videotapes (mini-DV format) will be stored in a locked cabinet in the *Motor Performance Laboratory* and will only be used for the purpose of this study.

9. POTENTIAL RISKS

Potential risks are no greater than that incurred by a normal office visit to a neurologist as this study is designed to be incorporated into the consultation. Patients may be inconvenienced by the extra 30 minutes required for consent and placement of markers.

10. POTENTIAL BENEFITS

No direct benefit to individual subjects is expected from this study. The potential benefits to this study are improved diagnostic accuracy and prediction of response to VP shunting in NPH patients. This may thus benefit future patients who are being evaluated for NPH and subsequent VP shunting.

11. ALTERNATIVES

This study is not a treatment protocol. Information is being collected for research purpose only. The alternative to participating in this study would be not to participate in either the infrared recording of movements or walking on the computerized Gait-Rite mat. Subjects will have the option to withdraw from the study at any time without explanation.

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