

Yale University

EliScholar – A Digital Platform for Scholarly Publishing at Yale

Yale Medicine Thesis Digital Library

School of Medicine

January 2014

Idiopathic Normal Pressure Hydrocephalus: A Review And A Proposed Role For

Conor Grady

Yale School of Medicine, conor.grady@yale.edu

Follow this and additional works at: <http://elischolar.library.yale.edu/ymtdl>

Recommended Citation

Grady, Conor, "Idiopathic Normal Pressure Hydrocephalus: A Review And A Proposed Role For" (2014). *Yale Medicine Thesis Digital Library*. 1882.

<http://elischolar.library.yale.edu/ymtdl/1882>

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Medicine Thesis Digital Library by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.

Idiopathic Normal Pressure Hydrocephalus: A Review and A Proposed Role for
Patient-Reported Outcomes

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By
Conor Wallis Grady

ABSTRACT

IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: A REVIEW AND A PROPOSED ROLE FOR PATIENT-REPORTED OUTCOMES.

Conor W. Grady (Sponsored by Charles C. Matouk). Department of Neurosurgery, Yale University, School of Medicine, New Haven, CT.

Despite nearly five decades of experience treating idiopathic normal pressure hydrocephalus (iNPH), there is still no consensus amongst care providers as to how to reliably identify patients with suspected iNPH who will benefit from shunt surgery, or how to measure post-operative symptom improvement. We performed a selective review of the literature, focusing especially on the role of neuroimaging in aiding in the diagnosis of iNPH, and the various clinical scales that have historically been used to assess outcome. Further, we tested the hypothesis that patient-reported outcomes (PROs) will demonstrate effectiveness of shunt surgery for the relief of iNPH symptoms consistent with that demonstrated through the application of clinical scales. To do this, we performed a retrospective analysis of one provider's experience treating patients with suspected iNPH, scoring outcomes based on patient-reported change in symptom severity. All patients treated for suspected iNPH between January 2012 and January 2014 with at least one month of follow-up and documented responses to direct questioning about pre- versus post-surgical symptom severity were included. Twenty-one patients were included in total. 100% of patients reported improvement in at least one of the three cardinal symptoms of gait disturbance, urinary incontinence, or cognitive impairment following shunt implantation. Gait, urinary, and cognitive symptoms individually improved 95%, 84%, and 89%, respectively. There was a significantly higher rate of improvement in any (i.e. at least one) symptom domain using PROs compared to historical data obtained through evaluation with clinical scales. There was no statistically significant difference between improvements in each individual symptom domain. PROs produce results that are largely consistent with data obtained by clinical scales, and can be used as one metric of patient improvement following shunt surgery for iNPH.

Acknowledgements

The existence of this thesis is owed entirely to my advisor and mentor, Dr. Charles Matouk. His guidance, advice, intelligence, and commiseration have been invaluable to my medical school experience. I must also acknowledge Drs. Charles Duncan and Murat Gunel, without whom my life would look radically different. I owe whatever success I have found or will find in large part to these three generous teachers.

I cannot fail to acknowledge the patients with iNPH in whose care I have had the privilege of participating, and whose outcomes are the subject of this research. As a patient population, they are an often-overlooked group, and they are owed higher quality research than what can be found in these pages – higher quality, for that matter, than anything that can currently be found in the literature. If this thesis accomplishes anything, I hope that it will shine a light on the incoherence in the present discourse on this disease, and possibly motivate someone more capable than myself to bring some standardization to the field.

Lastly, two personal acknowledgements:

First, I have to thank my parents for putting up with a dramatic decrease in the volume of our communication during the writing of this thesis. My mother rarely openly worried about me throughout the duration, and I know that this was not an easy feat for her. Both she and my father are and will always be the foundation of my every endeavor.

Finally, I would like to thank Catherine Chiabaut for her incredible patience. Unlike my parents, she was not spared contact with me during the writing process, and she endured me with a grace and kindness that was truly humbling. I count any warmth she may still have for me as my greatest accomplishment and dearest possession.

-C.W.G.

Table of Contents

Introduction	1
Review of the Literature	
• Methods	2
• Epidemiology	3
• Pathophysiology	4
• Diagnosis	4
• Clinical Features	5
• The Role of Neuroimaging	7
○ Anatomic and Volumetric Studies	7
○ Imaging of CSF Dynamics	11
○ Functional Neuroimaging	13
▪ Positron Emission Tomography	13
▪ Single-Photon Emission CT	15
▪ Dynamic Susceptibility Contrast MRI	16
▪ Functional Neuroimaging: Conclusion	17
○ Diffusion MRI	18
○ MR Spectroscopy	19
○ Neuroimaging: Conclusion	21
• Treatment	21
• Outcomes – Challenges	23
• Outcomes – Scales and Rating Systems	
○ Ordinal Scales	24
○ Improvement Indices	25
○ Validated Measures	26
○ Continuous Scales	27
• Outcomes – Results	29
• Review – Conclusion	31
Patient-Reported Outcomes in iNPH	
• Introduction	32
• Methods	
○ Patients	33
○ Evaluation	34
○ Results	36
○ Discussion	
▪ Patient Selection Rational and Patient Characteristics	38
▪ Comparison of Patient-Reported Outcomes to Historical Outcomes	40
▪ Comparison of Complete-Response Cohort and Incomplete-Response Cohort	41
▪ Limitations	42
▪ Conclusion	42
Appendix	44
References	52

Introduction

Normal pressure hydrocephalus (NPH) was first described in the English clinical literature in 1965 as a syndrome characterized by gait disturbances, cognitive impairment, and urinary incontinence in the setting of ventriculomegaly and normal opening pressure on lumbar puncture (1,2). Standard treatment for the disorder is the surgical diversion of CSF through the implantation of a shunt. Early clinical series reported questionable outcomes and high complication rates in shunt surgery for patients with NPH (3,4); in the decades that have followed, numerous studies have attempted to predict which patients will respond to shunting, leading to a proliferation of clinical scoring systems and proposed treatment algorithms (4-8).

NPH is categorized as either secondary or idiopathic. Secondary NPH has an identifiable etiology, such as subarachnoid hemorrhage or meningitis, while the etiology of idiopathic NPH remains unknown. The diagnosis of idiopathic NPH (iNPH) is complicated by the similarity of its clinical presentation to that of other neurological diseases typically affecting patients over 65, including Alzheimer's dementia and Parkinson's disease, which do not respond to CSF diversion procedures (9). Because of this, current guidelines recommend the categorization of patients into "probable", "possible", or "unlikely" iNPH based on clinical and radiological findings that have been associated with positive response to shunting (10,13). The diagnosis of iNPH is definitely made by improvement of the patient's symptoms following shunt surgery (13).

Despite the diversity of inclusion criteria and metrics for evaluating outcomes used by different studies, recent systematic reviews indicate that more than 70% of patients who receive a shunt for the treatment of iNPH will experience lasting improvement of at least one of their symptoms (14). As such, though little is known about its pathophysiology and no high quality studies have assessed the efficacy of shunting versus conservative management (15), there is evidence that iNPH is a clinical entity with an effective treatment.

In this thesis, I present a review of the current literature on iNPH, with an emphasis on the role of neuroimaging, patient outcomes, and the various outcome measures used. We additionally include an analysis of the experience in treating iNPH at Yale-New Haven Hospital, examining outcomes assessed by patient-reported primary end-points. The primary goal of this analysis was to investigate whether, in the absence of consensus means of evaluating outcomes in iNPH, using patient-reported endpoints will lead to a significantly different rate of response compared to the most recent rates reported in the literature. The secondary goal of this analysis was to examine if there are any patient characteristics that correlate with response to shunting for iNPH as assessed by patient-reported end-points.

Review of the Literature

Methods

The review presented in this thesis is based on a selective review of the literature, including the most recent English-language guidelines (10-13), select review articles

published since 2001, and original literature retrieved by a search of PubMed. As there is no level 1 data on the treatment or diagnosis of NPH, all clinical data summarized are level 2 or 3. Level of evidence is determined using the system established in the most recent international guidelines (15).

Epidemiology

Little is known about the prevalence and incidence of iNPH, as reported figures vary widely. A door-to-door survey of 982 individuals older than 65 resulted in a reported prevalence of 0.41% (17). Examining neurosurgical referrals in a stable Norwegian population, prevalence appeared to be highly age dependent, ranging from 3/100,000 in those aged 50-59 to 181.7/100,000 in those 70-79 (18). This same study reported an overall incidence of 5.5/100,000. A random sampling of a Japanese population aged 65 years or older found the prevalence of iNPH to be 1.4% as diagnosed by ventriculomegaly on neuroimaging and at least one element of the classical clinical triad of gait disturbance, cognitive impairment, or urinary incontinence (19). In a population of assisted-living and extended-care facility residents, incidence ranged from 9% to 14% (20). All of these studies acknowledged that their findings were highly dependent on the diagnostic criteria used.

Another important consideration in the epidemiology of iNPH is its rate of comorbidity with other neurologic disease. In a study of 28 patients with iNPH diagnosed by clinical, radiological, and CSF dynamic criteria, 89% had pathologic findings consistent with some neurologic disease, and 78% had evidence of Alzheimer's disease, cerebrovascular

disease, or both (21). Others have reported biopsy-confirmed Alzheimer's disease in as many as 75% of patients undergoing shunt placement for treatment of iNPH (22). Such data are significant, as it has been hypothesized that patients with dementia not entirely attributable to iNPH may still experience resolution of gait and urinary symptoms following shunting (23).

Pathophysiology

The exact pathophysiological mechanism by which iNPH arises is unknown. The most common pathological findings in iNPH are evidence of Alzheimer's disease and cerebrovascular disease; there are no pathologic findings specific to iNPH (13).

Numerous etiologies have been proposed for iNPH, with the majority attributing the disease to a combination of periventricular ischemia and disturbed CSF fluid dynamics (24). Current hypotheses include mechanical compression of the brain parenchyma by dilated ventricles, accumulation of toxic metabolic products as a result of decreased CSF turnover, and periventricular microvascular damage caused by increased arterial pulsations (25).

Diagnosis

Since its discovery, multiple criteria have been proposed for the diagnosis of NPH, ranging from positive response to shunt placement (26) to the presence of only one of the classic triad of symptoms with radiologic confirmation of communicating hydrocephalus (27). Because of the absence of a consensus set of diagnostic criteria, a considerable amount of research has been devoted to determining which patients are most likely to

respond to shunting (4-8). The information provided by these studies has been synthesized into international guidelines, which recommend that patients be diagnosed with “probable”, “possible”, or “unlikely” hydrocephalus based on a combination of clinical and radiological findings associated with positive response to shunt placement (10,13). One set of guidelines still reserves a definitive diagnosis of iNPH for those who show improvement of symptoms with shunting (13).

Clinical Features

The full syndrome of gait disturbance, cognitive impairment, and urinary incontinence may be present in as few as 51% of patients with probable iNPH (28). At least one component of the triad, however, is essential to the diagnosis of the disease.

Gait impairment is the most common presenting symptom, though it may be subtle early in the course of the disease. The gait disturbance seen in iNPH is characterized by imbalance, short steps, broad stance, difficulty turning, and outward rotation of the feet. It does not improve with visual or auditory cues, unlike a Parkinsonian gait. Apraxia is rarely a component of the gait disturbance typical of iNPH (29). Depending on the precise diagnostic criteria applied, between 94% and 100% of patients with iNPH will have gait disturbances (13). Both sets of English-language guidelines have prominent gait disturbance as an essential feature of probable iNPH (10,13).

The cognitive dysfunction seen in iNPH is typically frontal-subcortical in nature. Its most prominent features are impaired executive function, impaired concentration and attention,

psychomotor slowing, and impaired working memory (23,30). Recall memory is typically preserved. Features of cortical dementia such as gross amnesia, disorientation, and aphasia are decreased relative to the cognitive impairment typical of Alzheimer's disease (30). Cognitive impairment is seen in 78% to 98% of patients with iNPH (13).

The urinary symptoms of iNPH range from increased urinary frequency to gross incontinence. The underlying cause of the urinary symptoms is detrusor hyperactivity resulting from a reduction of central inhibitory control (31). Patients typically progress from increased frequency, to urge incontinence, and finally to frank urinary incontinence. Of note, bowel incontinence is extremely rare in iNPH, and is likely indicative of progressive frontal lobe dysfunction rather than further loss of central control over sphincter function (23).

Average CSF opening pressure in patients with iNPH is mildly elevated relative to healthy individuals (32), but by definition must be below either 18cm H₂O or 20cm H₂O, depending on the diagnostic criteria used (10,13).

In the patient's history, age greater than 65, insidious onset, and progression of symptoms are consistent with a diagnosis of iNPH (10). An identifiable etiology of the hydrocephalus excludes a diagnosis of iNPH.

The Role of Neuroimaging

Radiologic evidence of hydrocephalus is essential to the diagnosis of iNPH.

Traditionally, an Evans index (33) greater than 0.3 on CT or MRI has been the standard for the diagnosis of ventricular enlargement (10). This, in combination with the absence of evidence of CSF flow obstruction, constitutes the minimum radiologic indication of iNPH. Beyond this, however, there is considerable debate as to what other neuroimaging findings might be of use in the diagnosis and evaluation of iNPH. In the sections that follow, I will discuss ways in which various imaging modalities have been used to assess patients with suspected iNPH and assess their role in clinical practice.

Anatomic and Volumetric Studies

Since the advent of modern neuroimaging, numerous studies have attempted to identify anatomical and volumetric findings on conventional CT and MRI that could serve as diagnostic or prognostic markers for iNPH. One of the earliest such studies, by Borgsen and Gjerris (34), interrogated the possible connection between the degree of ventricular dilation as measured by the Evans index, the size of cortical sulci, and the presence or absence of periventricular lucencies with outcome following shunting in patients with suspected NPH. Sixty-four patients with either iNPH or secondary NPH who met the criteria of 1) presenting with the full triad of cardinal symptoms 2) symptom duration of greater than three months and 3) CT-confirmed ventriculomegaly were treated with ventriculo-atrial shunts. Their outcomes were then correlated with their findings on CT. Ventricular size was not significantly associated with outcome, but both small cortical

sulci and the presence of periventricular lucencies were identified as predictors of positive response to shunting (34).

In the decades since the publication of Borgsen's and Gjerris's work, the proliferation of low-powered studies proposing radiologic findings with either diagnostic or prognostic value in the evaluation of iNPH have resulted in an inconsistent body of literature. Some findings, such as hippocampal atrophy, have been demonstrated in patients with iNPH relative to healthy controls, but are also known radiologic features of other neurodegenerative diseases, and are therefore of limited diagnostic significance (35). Others, such as the periventricular lucencies identified by Borgsen and Gjerris, have failed to consistently demonstrate their proposed utility as predictors of outcome (36,37). Still others have been complicated by revision, such as the discovery that limited areas of focal sulcal dilation in the setting of generally small cortical sulci could be observed in patients ultimately diagnosed with shunt-responsive iNPH (38). As a result, though there are many radiologic findings generally believed to be useful in the diagnosis or evaluation of iNPH, there is presently no consensus to what extent or in what way these findings should influence clinical practice.

Despite this, many recent studies continue to attempt to identify additional anatomical and volumetric markers in suspected iNPH. A recently investigated anatomic marker is the callosal angle, which is measured between the lateral ventricles in a coronal image taken through the posterior commissure and oriented perpendicular to the anterior commissure-posterior commissure plane. As a diagnostic aid, Ishii and colleagues

demonstrated that patients with iNPH had significantly smaller callosal angles than either patients with Alzheimer's dementia or healthy controls (39). Using a cutoff of 90° , they were able to distinguish iNPH from Alzheimer's dementia with an accuracy, sensitivity, and specificity of 93%, 97%, and 88%, respectively. When they added to this the requirement of an Evans index of 0.3 or greater, their results improved to 96%, 97%, and 94% (39). Virhammar, *et al.*, investigated the callosal angle as a predictor of outcome following shunt surgery. Looking at 108 patients who received shunts for suspected iNPH, they found that patients with shunt-responsive iNPH had significantly smaller callosal angles than did patients whose symptoms did not respond to shunt surgery (59° versus 68°). Using ROC analysis, they determined an optimal cutoff of 63° , resulting in a sensitivity and specificity of 67% and 65%, respectively (40).

Volumetric analyses have likewise yielded a variety of results. With respect to predicting surgical outcomes, one study of 26 patients with suspected iNPH failed to demonstrate any significant difference in mean ventricular volume ratio, mean brain volume ratio, mean pericerebral CSF volume ratio, or mean ventricular/pericerebral CSF volume ratio between shunt-responders and non-responders (41). Looking at compartmental variations in CSF volume, another group demonstrated that 11 patients with shunt-responsive iNPH had increased CSF volume in the lateral ventricles and Sylvian fissures, but decreased CSF volume in the superior convexity and medial subarachnoid spaces compared to patients with Alzheimer's dementia and age-matched, healthy controls (38). Building on these findings, a multicenter, prospective study selected 100 patients for shunt surgery based on clinical presentation consistent with iNPH and MRI findings of tight superior

convexity and medial subarachnoid spaces with enlarged Sylvian fissures and ventriculomegaly, a constellation of imaging findings collectively referred to as Disproportionately Enlarged Subarachnoid-space Hydrocephalus (DESH). At one year following surgery, 69% of patients demonstrated improvement of 1 point or more on the modified Rankin Scale, and 89% had demonstrated improvement at some point during the year (42).

In a prospective study of 43 patients with suspected iNPH, Lee and colleagues simultaneously investigated the connection between many of the proposed anatomic and volumetric markers of iNPH and response to CSF tap test. Frontal convexity narrowing, parietal convexity narrowing, empty sella, upward bowing of the corpus callosum, and narrowing of convexity with dilation of sylvian fissure CSF spaces (i.e. DESH) were all compared against patient response to the removal of 40ccs of CSF via lumbar puncture. Of these, both an empty sella and DESH were significantly linked to positive response to CSF tap test, with the presence of either of the two signs corresponding to a sensitivity, specificity, positive predictive value, and negative predictive value of 72.7, 81, 80, and 73.9%, respectively (43).

International guidelines have attempted to synthesize the literature on anatomic and volumetric findings in iNPH. The 2005 guidelines authored by the NPH independent study group listed callosal angle, temporal horn size, and periventricular lucencies as radiologic findings worth assessing when considering a diagnosis of iNPH (10). More recently, the updated guidelines of the Japanese Neurosurgical Society, published in

English in 2012, did not list any anatomic findings, listing instead only those volumetric findings consistent with DESH as radiologic findings indicative of iNPH (13).

Of note, though there are no anatomic or volumetric radiologic findings that can confirm a diagnosis of iNPH or predict a patient's response to shunting, several studies have indicated that there are also no radiologic findings that should prevent a patient with suspected iNPH from being considered for shunt implantation. Specifically, deep white matter lesions representing hypertensive or lacunar infarcts are not predictive of a poor response to shunting, and therefore should not rule out a diagnosis of iNPH (44,60).

Imaging of CSF Dynamics

Abnormal CSF dynamics are believed to contribute to the pathogenesis of iNPH (24). As such, analysis of CSF flow using phase-contrast MRI has been investigated for potential diagnostic and prognostic information in the assessment of patients with suspected iNPH. Early studies were promising; a chart review of twenty patients, with eleven followed up to five years after shunt surgery, showed a significant correlation between increased aqueductal CSF flow void and good or excellent outcome (45). A later prospective study by the same author, however, failed to recreate this finding, while identifying CSF stroke volume through the cerebral aqueduct greater than 42 μ L as a predictor of shunt-responsiveness (46).

Subsequently, better-powered, better designed studies have failed to find significant differences in either CSF flow void intensity or CSF stroke volume between either shunt

responders and non-responders amongst patients with suspected iNPH, or between iNPH patients and patients with other forms of dementia. In a prospective trial of 49 patients shunted for suspected iNPH, CSF flow through the cerebral aqueduct did not significantly correlate with clinical outcome (47). Another study comparing patients with a clinical diagnosis of iNPH to patients with early Alzheimer's dementia, patients with early vascular dementia, and healthy controls found that there was no difference in aqueductal stroke volume between the groups (48).

More recent studies have continued to interrogate CSF stroke volume, while also investigating additional CSF dynamic parameters. In a retrospective study, Forner-Giner and colleagues stated that increased average CSF flow of 18.2mL/min and increased mean CSF stroke volume of 138.7 μ L were both 100% specific and 86% and 79% sensitive, respectively, at correctly identifying patients with shunt-responsive iNPH from patients with ischemic cerebrovascular disease (ICD) or healthy controls (49). It should be noted, though, that the cohorts in this study were unequal (61 healthy, 19 ICD, 24 NPH) and were not age-matched.

The diverse and occasionally contradictory nature of the results of these studies has been hypothesized to be the result of a high degree of variability in technique in image acquisition and data analysis between institutions (50). As such, both the diagnostic and prognostic value of phase-contrast MRI measurements of CSF fluid dynamics in the evaluation of patients with suspected iNPH is highly uncertain at present.

Functional Neuroimaging

Functional imaging modalities measuring blood flow and metabolism can provide insight into regional patterns of activity or dysfunction within the brain. As abnormal cerebral blood flow (CBF) is thought to contribute to the pathogenesis of iNPH, a number of different types of functional imaging have been investigated for possible utility in the assessment of patients with iNPH. Below, we will discuss these various imaging methods and evaluate their role in guiding clinical decision making.

Positron Emission Tomography (PET)

One of the earliest studies examining the potential role of functional imaging in the treatment of iNPH investigated whether or not iNPH could be distinguished from Alzheimer's dementia based on patterns of cortical metabolism. Three patients with NPH, seventeen with Alzheimer's disease, and seven age-matched controls were compared to one another on the basis of fluorine-18-labeled fluorodeoxyglucose (^{18}F -FDG) utilization. Both the iNPH and Alzheimer's groups showed reduced cortical metabolism relative to controls. The pattern of hypometabolism differed between the two groups, however; Alzheimer's patients demonstrated a pattern of bitemporal hypometabolism, while NPH patients showed a global reduction in cortical glucose use (51).

Subsequently, Momjian, Owler, and colleagues expanded on these findings by using ^{15}O -H₂O PET to identify the thalami, basal ganglia, and periventricular regions as areas of decreased CBF in patients with iNPH relative to healthy controls (52,53). Klinge and

colleagues also demonstrated a correlation between decreased regional CBF in the medial frontal lobes and anterior medial temporal lobes as measured by ^{15}O -H₂O PET, and pre-surgical symptom severity in patients with a clinical diagnosis of iNPH. In this same study, they also showed a significant difference between shunt responders and non-responders with respect to increased medial frontal lobe CBF following shunt surgery, though there was no significant difference in regional CBF between these two groups' pre-operative studies (54).

Calcagni, *et al.*, recently performed a prospective study of the change in regional cerebral metabolic rate of glucose (CMRglu), as measured by ^{18}F -FDG utilization, following shunt surgery in 20 patients with clinically diagnosed iNPH. Following shunting, the 17 patients who improved demonstrated globally increased CMRglu relative to their pre-surgical studies. In contrast, the three non-responders only showed increased CMRglu in the left frontal cortex, left putamen, and right thalamus, respectively. Notably, there was no difference in CMRglu between shunt responders and non-responders on pre-operative exam. There was, however, a statistically significant correlation between the magnitude of increase in CMRglu and degree of clinical improvement between individual shunt-responders' pre- and post-operative studies (55).

Though numerous studies have demonstrated post-operative changes in patterns of cerebral metabolism and blood flow, no studies to date have found any ability of PET to predict clinical outcome following shunt surgery in patients with suspected iNPH.

Additionally, studies demonstrating findings of potentially diagnostic regional

hypometabolism or hypoperfusion have used small cohorts. Though studies utilizing PET offer a promising glimpse into possible mechanisms of pathogenesis in iNPH, they have done little to establish PET's clinical utility.

Single-Photon Emission CT (SPECT)

Early studies attempting to correlate patterns of regional CBF visualized by SPECT with diagnosis or outcome following shunting in patients with suspected iNPH offered promising results. In a study of 22 patients who received shunts following a clinical diagnosis of iNPH, Graff-Radford and colleagues found that an anterior/posterior CBF ratio cutoff of 1.05 was able to correctly classify the outcome in 19 of the cases; all but one of the patients who did not respond to shunting had anterior/posterior CBF above 1.05, while all but two of the patients who responded to shunting had ratios below this threshold (56). This same group subsequently recreated these findings, showing that increased anterior/posterior CBF ratio correlated with increased likelihood of a non-response to shunting in patients with suspected iNPH (57).

In a study of 37 patients with suspected iNPH, Chang, *et al.*, demonstrated decreased mean CBF relative to age-matched healthy controls. This same study showed that patients who responded to shunting, while still possessing lower mean CBF than controls, had higher CBF than patients with suspected iNPH who did not respond to shunting (58).

More recent studies have failed to reproduce these promising initial results. A study of 84 patients with iNPH as diagnosed by DESH criteria found three patterns of reduced

regional CBF relative to healthy controls. Specifically, 58% of patients showed anterior-dominant reduction in CBF, 12% showed posterior-dominant reduction, and 30% had mixed or diffuse-type reduction. Though the finding of predominantly anterior reduction in CBF in the majority of patients would seem to support the earlier finding of a relatively lower anterior/posterior CBF ratio in shunt-responders, there was no significant difference in responsiveness to shunting between the three types, which responded at rates of 83, 90, and 84%, respectively (59). A similar pattern and patient distribution of anterior-, posterior- and mixed-type reduced CBF was seen in a more recent study, which also showed no link between the pattern of reduced CBF and outcome (60).

While SPECT has consistently demonstrated patterns of reduced CBF in patients with suspected iNPH relative to healthy individuals, the largest and most recent studies investigating the utility of the modality as a prognostic or diagnostic tool have failed to show a significant link between SPECT findings and patient outcome.

Dynamic Susceptibility Contrast MRI

Relatively few studies have attempted to use MR perfusion studies to identify diagnostic or prognostic markers of use in the assessment of patients with suspected iNPH. The largest and most recent of these was a prospective study conducted by Zieglitz, *et al.*, in which dynamic susceptibility contrast MRI findings in user-selected regions-of-interest were compared in 21 patients with the clinical diagnosis of iNPH and 16 age-matched healthy controls. All members of the iNPH cohort were then shunted, and pre- and post-operative imaging studies of shunt responders and non-responders were compared.

Patients with iNPH demonstrated significantly reduced regional CBF in the basal medial frontal cortex, the hippocampus, the lentiform nuclei, and all regions of the periventricular white matter compared to healthy controls. With respect to outcomes, shunt responders demonstrated a greater reduction in CBF of the periventricular white matter compared to non-responders, which fit with the additional finding that the magnitude of reduction of CBF to the periventricular white matter seen on pre-operative studies was directly correlated with symptom severity, and patients with worse symptomatology at the time of shunting received more obvious benefit from CSF diversion. Non-responders had reduced CBF of the basal medial frontal cortex relative to shunt responders (61).

Further study is needed to establish the clinical role for MR perfusion studies in the assessment or management of iNPH. Presently, however, it is a modality that potentially offers insight into the pathogenesis of iNPH while further elucidating the findings of other functional imaging studies.

Functional Imaging: Conclusion

In a 2001 review, Owler and Packard noted that measures of CBF had failed to improve either the diagnostic or prognostic accuracy of the assessment of patients with suspected iNPH, largely due to center-specific technical and methodological differences (62). More than a decade later, this is still the case. Though functional imaging continues to be a valuable research tool, there are presently no diagnostic or prognostic markers of reliable clinical utility.

Diffusion MRI

The clinical utility of diffusion MRI has been the focus of a number of studies in recent years. Studies attempting to identify diagnostic markers by diffusion tensor imaging (DTI) have produced especially consistent results. Kim and colleagues looked at differences between 16 patients with shunt-responsive iNPH relative to 10 patients with Alzheimer's dementia, 10 patients with vascular dementia, and 20 healthy controls using region-of-interest-based DTI. The iNPH patients were found to have higher fractional anisotropy (FA) in the posterior limb of the internal capsule (PLIC) relative to the all other cohorts. Using ROC analysis to arrive at an optimal cutoff value of 0.613, the authors were able to identify iNPH relative to either healthy controls or other dementia patients with a sensitivity and specificity of 87.5% and 95.0%, respectively (63). Another recent study used DTI to compare a cohort of 24 patients with a clinical diagnosis of iNPH to 20 healthy controls, and also found significantly higher FA in the PLIC of iNPH patients (64). This study found a considerably more significant decrease in FA in the corpus callosum of iNPH patients relative to healthy controls, however, and was able to correlate lower FA in the corpus callosum with worse gait symptomatology at presentation. Both of these studies support an earlier finding by Hattingen, *et al.*, that patients with iNPH have higher FA in the periventricular corticospinal tract, and lower FA in the corpus callosum (65).

Aside from these findings, other diagnostic markers of iNPH on DTI have been proposed, including fornix length (66) and specific patterns of intracranial mean diffusivity (67), but these have yet to be reproduced by other studies.

Previous studies have reported that patients with NPH had increased apparent diffusion coefficient (ADC) in the periventricular white matter (68). In a study of 11 patients with a clinical diagnosis of iNPH, Corkill, *et al.*, investigated the ability of periventricular white matter ADC to predict patients response to shunting. Patients who did not improve with shunting were found to have significantly higher periventricular white matter ADC when compared both to shunt-responsive iNPH patients and age-matched healthy controls (69). More recently, it has been demonstrated that increased changes in ADC with each cardiac cycle can be of use in distinguishing iNPH from both healthy controls and patients with Alzheimer's and Parkinson's diseases (70,71).

Diffusion MRI may provide diagnostic markers, especially on DTI, though these findings need to be validated in larger studies. The ability of diffusion MRI to predict patient outcome to shunting in cases of suspected iNPH is difficult to assess given the limited number of studies investigating the topic.

MR Spectroscopy

MR spectroscopy (MRS) enables investigators to search for distinguishing patterns of regional metabolite concentration in the brains of patients with likely iNPH. One early study attempting to differentiate various dementia syndromes from on the grounds of MR

spectroscopic data found that, of the syndromes investigated, only iNPH had potential marker on MRS (72). This marker, an increased lactate/creatinine ratio in intraventricular CSF, was also identified in a small cohort study conducted by Kizu and colleagues (73).

More recent studies have investigated the relative concentrations of various metabolites within the brain parenchyma. In a prospective study comparing 24 patients diagnosed with iNPH on the grounds of clinical presentation, radiographic findings, and positive tap test, 11 patients with other forms of dementia, and 20 healthy controls, both iNPH and otherwise demented patients had decreased N-acetyl Acetate(NAA)/creatinine and NAA/choline ratios in their white matter relative to the control group. No significant difference was seen between the iNPH and other demented patients, and no significant correlation was found between MRS findings and response to shunting within the iNPH cohort (74). A similar finding was reported by Lundin, *et al.*, who discovered decreased NAA levels in the thalami of patients with a clinical diagnosis of iNPH compared to age-matched healthy controls (75). It should be noted, however, that Lundin, *et al.* showed decrease NAA in the thalami; there was no difference in NAA concentration between iNPH patients and controls in any other regions examined, including those investigated by the earlier study.

The clinical role of MRS is uncertain at this time. Though some patterns of metabolite concentration in both CSF and brain parenchyma seem to correlate with a diagnosis of iNPH, the studies demonstrating these are small, and their findings are not sufficiently consistent across studies to allow any conclusions to be drawn.

Neuroimaging – Conclusion

The role of various imaging modalities in the evaluation of patients with suspected iNPH is an ongoing area of significant investigation. Presently, no single imaging modality can provide clinicians with definitive diagnostic or prognostic information.

Treatment

The discovery of NPH was defined by improvement of patients' dementia following the diversion of CSF through the surgical placement of a shunt (2). Presently, shunt surgery remains the mainstay of treatment for iNPH; some diagnostic criteria even require a response of a patient's symptoms following shunt placement for the diagnosis of definitive iNPH to be made (13).

In the late 1990s, endoscopic third ventriculostomy (ETV) was proposed as an alternative to shunt surgery for the treatment of iNPH (76). One multicenter study showed outcomes equivalent to those seen in patients treated with shunt surgery, with 69% of patients treated with ETV showing some improvement at 24 months after surgery (77).

Subsequent studies demonstrated similar outcomes, though improvement was most significant in younger patients and in those with increased resistance to ventricular CSF outflow (78,79).

Two recent studies have examined the relative safety and effectiveness of shunt surgery and ETV in the treatment of iNPH. A robust, population-based study used a national

database of the ICD-9 discharge codes for ETV and shunt surgery in patients diagnosed with iNPH to investigate the perioperative mortality and complication rate for each procedure. The findings showed ETV to have a perioperative mortality rate of 3.2% and a complication rate of 17.9% compared to a mortality rate of 0.5% and a complication rate of 11.8% in shunt surgery (80). Additionally, a randomized, parallel, open-label trial showed superior outcomes in patients treated with shunt surgery versus those treated with ETV; 76.9% of patients treated with shunt surgery showed some improvement 12 months after their procedure compared to 50% of those who underwent ETV (81). These studies indicate that shunt surgery is presently a safer and more effective treatment than ETV for iNPH.

The role of conservative management in patients with suspected iNPH has not been well characterized. There is currently a double-blind, randomized, controlled trial assessing conservative management versus shunt surgery underway, but it has yet to announce any findings (82). One systematic review of the literature showed that a small number of patients with suspected iNPH may improve without surgical treatment, but that more than half of patients showed measurable deterioration in at least one of their symptoms three months after initial evaluation (83). A recent retrospective review compared serial pre- and post-operative exams of patients who had waited at least six months for shunt surgery after receiving a clinical diagnosis of iNPH to similar exams of patients who had received shunt surgery within three months of receiving their diagnosis. The delayed shunting cohort experienced significant decline in all symptom categories except for incontinence in the months prior to their surgery, and their post-operative improvement, while

significantly improved over their last pre-operative exam, was significantly worse than the outcomes in the more rapidly shunted cohort (105).

Presently, shunt surgery remains the treatment of choice for patients with iNPH. Current trials comparing conservative management to shunting will have the dual benefit of revealing what role conservative management should play in the treatment of iNPH, as well as providing level 1 data on shunt surgery's effectiveness as a treatment for the disorder. The limited data that is available indicates that earlier shunting in patients with suspected iNPH may prevent further progression of the patients symptoms.

Outcomes – Challenges

The response of gait, urinary, and cognitive symptoms to shunt surgery has been central to both the discovery and subsequent decades of diagnosis of NPH. Despite this, there is no consensus metric by which improvement in these symptoms following shunting is measured. Numerous studies either measuring outcomes or attempting to predict which patients are most likely to respond to shunting have used a vast number of different clinical scales to assess pre- and post-shunting symptom severity. These studies have also employed a variety of inclusion criteria as a result of the absence of a single diagnostic marker for iNPH other than response to shunting. As a result, comparing outcome measures across studies is complicated, requiring careful attention be paid to the clinical scales used in each study, the inclusion criteria employed by each study, and each study's threshold for scoring an outcome as a positive response to shunting.

In the sections that follow, I will first describe some of the types of clinical scales encountered in the literature on iNPH. I will then discuss outcomes as reported in the literature. An accompanying evidentiary table will outline which scales were used by selected studies, each study's inclusion criteria, and the criteria by which each study scored an outcome as a positive response to shunting.

Outcomes – Scales and Rating Systems

Ordinal Scales

Ordinal scales, in which a patient's symptoms are assigned a ranking according to their severity, were amongst the first rating systems used in the evaluation of treatment outcomes in iNPH. The symptom severity score in these scales is assigned based on the evaluating clinician's assessment of the patient. One of the oldest rating systems still in use is the scale devised by Stein and Langfitt (3). This scale assigns a patient's overall symptomatology a score between 0 (no deficit) and 4 (patient requires full custodial care). The clinical scale devised by Black (4) is similar to the Stein-Langfitt scale, as it scores the patient's overall symptomatology without distinguishing between specific symptoms. Unlike the Stein-Langfitt scale, which enables the comparison of pre- and postsurgical scores, the Black scale directly rates a patient's response to treatment; a grade of "poor", "transient", "fair", "good", or "excellent" is assigned based on the extent and duration of improvement seen in a patient with iNPH's symptoms following shunting.

Ordinal scales that evaluate each symptom of iNPH separately have also been used (88,89,90,91,92,94). Though the criteria for specific rankings of symptom severity differ from scale to scale, they all require individual scoring of at least gait disturbance, cognitive impairment, and urinary incontinence. These specific symptoms scores are then summed to provide a final iNPH score. As with the Stien-Langfitt, and Black scales, the symptom scores are determined by the judgment of the assessing physician.

These scales are easy to employ and provide a general picture of the severity of a patient's disease. They are widely used and are the most common outcome assessment tool encountered in the iNPH literature. A major disadvantage of these scales, however, is that they are supported by few objective measures and rely heavily on the assessing clinician's judgment. To address this, the creators of one scale demonstrated significant interrater reliability ($\kappa = 0.76 - 0.85$) when comparing a small number of expert raters, though they cautioned that physicians less familiar with the treatment of iNPH would likely need additional training before employing their scale (94). As such, there are questions regarding the external validity of studies relying solely on ordinal scales to assess patient outcome (100).

Improvement Indices

To facilitate more direct assessment of outcomes, at least two different improvement indices have been proposed. Both begin with the scoring of either symptom severity or improvement on an ordinal scale. The Krauss Improvement Index (85) scores symptom improvement following shunting as 0 (no improvement), 1 (fair or good improvement),

or 2 (excellent improvement). The sum of these improvement scores is then divided by the two times the number of cardinal symptoms present prior to shunting. The end result is a number between 0 and 1, with 0 indicating no improvement in any symptom, and 1 indicating excellent improvement in all symptoms. The NPH Recovery Rate, proposed by Kiefer, *et al.* (89), begins with the calculation of pre- and post-surgical ordinal scale ranking comprised of the sum of individual symptom scores. The NPH Recovery Rate is then calculated by subtracting the pre- and postsurgical ordinal scores, dividing the result by the presurgical score, and finally multiplying by ten - the larger the resulting NPH Recovery Rate, the more significant the improvement in the patient's symptoms.

Though these indices allow investigators to present the extent of a patient's improvement with a single number, they do not provide any information that is not available prior to their calculation. In the case of the Krauss Improvement Index, outcome assessment can be made from the ordinal outcomes score assigned to each symptom. The difference between the pre- and postoperative ordinal scores in the numerator of the NPH Recovery Rate also allows for assessment of outcome without any further calculation. Additionally, these indices are limited by the reliability of the ordinal scales on which they are based.

Validated Measures

Other studies have assessed functional outcome or symptom severity using scales validated in diseases other than iNPH. The Barthels ADL Index and Modified Rankin Scale, both validated in the assessment of patients recovering from stroke, have been used to gauge overall functional status in patients with iNPH (28,86,87,93,99). Many

studies have evaluated the cognitive symptoms of iNPH using the Mini Mental State Exam, which was validated as a screening test for dementia in elderly patients (8,28,84,86,87,94,95). Numerous other psychometric tests have also been employed to allow for more precise identification of a patient's cognitive dysfunction (12). Likewise, symptom specific tests for gait disturbance, such as the timed-up-and-go test, and urinary incontinence, such as the International Consultation on Incontinence Questionnaire – Short Form, have been used to evaluate the severity of those symptoms in iNPH (28,94,95).

The use of validated tests addresses some of the limitations of iNPH-specific ordinal scales, such as uncertain external validity. It should be noted, however, that, as these scales were validated for the evaluation of diseases other than iNPH, their generalizability needs to be examined. For example, the frontal-subcortical dysfunction that is characteristic of the cognitive impairment in iNPH may not be detected by the Mini Mental State Exam, which was validated for the assessment of Alzheimer's type, cortical dementia (101).

Continuous Scales

Recently, Hellstrom, *et al.* proposed a continuous iNPH rating scale based on a combination of ordinal and objective assessments of gait, neuropsychology, balance, and continence (102). Each symptom is scored from 0-100, with a score of 100 corresponding to the performance observed in an age-matched healthy population. The gait and neuropsychologic scores are the average of scores arising from both ordinal ranking and

objective assessment of symptom severity. For example, the final gait score is the average of three separate scores, each ranging from 0-100: an ordinal ranking, the number of steps required to walk 10m, and the time in seconds required to walk 10m. The balance and continence scores are provided by ordinal scales alone. The final iNPH score is the mean of the symptom scores, provided by the equation $[(2 \times \text{gait}) + (\text{neuropsych}) + (\text{balance}) + (\text{continence})] / 5$ (or number of scores available). It should be noted that the gait score is given twice the weight of the other symptom scores, and that the denominator will change depending on the number of symptoms assessed at the time of testing. The creators of this scale further recommend a minimum improvement of 5 points in the overall iNPH score as indicative of a response to shunting.

This scale attempts to address some of the limitations inherent in simple ordinal scales through the inclusion of objective criteria for assessing gait and neuropsychologic functioning. Hellstrom and colleagues also assert that their scale is calibrated such that a score of 100 represents the performance of a healthy individual and lower scores provide an empiric basis for comparison of iNPH scores between patients – for example, a score of 50 corresponds to the 50th percentile of symptom severity. A significant limitation of this scale, however, is that it takes significantly longer to administer – 30 to 40 minutes total – compared to assessment with an ordinal scale. Additionally, two of its components, balance and continence, are rated by ordinal scales alone. Though these were shown to correlate significantly with the gait and neuropsychologic scores, they are still limited by the reliability of the scales on which they are based.

Outcomes – Results

Reported outcomes have varied widely. The most recent international guidelines quote an overall shunt response rate between 30-96% (12). In formulating their most recent guidelines, the Japanese Neurosurgical Society encountered 3-6 month improvement rates following shunting of 64-96%, 1-year improvement rates of 41-95%, and 3-5 year improvement rates of 28-91% in their review of the literature (13). A more recent review of the literature found that in all studies of iNPH outcomes published since 2006, improvement rates at 3 months, 1 year, and greater than 3 years were 81%, 82%, and 73%, respectively (16).

Improvement rates also vary between elements of the iNPH symptom triad. Gait is the most likely symptom to improve, with response rates in cognitive impairment and urinary incontinence both highly variable depending on the scales used to assess recovery. Overall response rates for the symptoms have been reported between 58-90%, 29-80%, and 20-82.5%, respectively (13).

The most recent data indicate that many patients' symptoms will demonstrate long lasting improvement following shunting for iNPH. A comparison of reviews of outcomes in patients who had shunts implanted for the treatment of iNPH demonstrates a trend toward better long term symptom improvement over the past 13 years; a 2001 review found that 29% of patients experienced "prolonged or significant improvement" (103), while a 2013 review reported that 73% of patients showed some improvement at 3 years or longer following surgery (16). One recent study investigating long-term symptom improvement

found that 90% of patients will report some improvement in at least one symptom at 5 years following shunting, and 87% will continue to report improvement at 7 years (95). Another study reported an average Krauss Improvement Index of 0.70 at an average follow-up of 80.9 months after shunt surgery (97).

Complication rates related to shunts in patients with iNPH have historically been high, with early series quoting complication rates as high as 35%, including an 8% mortality rate (4). A recent review showed that, since 2006, the overall complication rate of 21.4%, with a 0.2% mortality rate. The most common complication found by this review was need for later shunt revision, which accounted for 61% of all reported complications. The remaining complications were subdural hematoma, intracerebral hemorrhage, and shunt infection, which accounted for 20%, 1%, and 18% of all complications, respectively (16).

Previous guidelines have emphasized the importance of weighing an individual's risk-benefit ratio when considering a patient with suspected iNPH for shunt surgery (10). To examine this, a computer model, using data acquired through a review of the literature current to 2005, ran a Monte Carlo simulation over a wide range of risk and benefit parameters. Their model case was a 65 year-old with suspected iNPH and mild to moderate Alzheimer's type dementia. The simulation ran 1000 trials with 1000 patients each. The resulting data indicated that the complication rate would have to exceed 50% before liberal shunt implantation would cause more harm than benefit as measured by QALYs gained in the trial's model population (104).

Review - Conclusion

The comparison of studies investigating normal pressure hydrocephalus is complicated by an absence of both a consistently applied set of diagnostic criteria and a consensus means of measuring patient outcomes following shunt surgery. Despite this, the most recent data indicates that a majority of patients with iNPH will experience potentially long-term improvement of at least one aspect of their syndrome with shunt implantation.

Though careful patient selection should remain at the center of all surgical decision-making, the trends over the past decade with respect to shunt surgery in patients with suspected iNPH have been of decreasing risk and increasing effectiveness. It is likely that more patients with suspected iNPH would benefit from earlier shunting (104), and that even patients with significant medical and neurologic comorbidity would experience some benefit from CSF diversion (90,91,98,99).

Patient-Reported Outcomes in iNPH

Introduction

In the absence of consensus diagnostic criteria or methods of measuring outcomes, the effectiveness of CSF diversion via surgical implantation of a shunt remains difficult to assess with certainty. Despite this, as demonstrated by the preceding review of the literature, the preponderance of evidence indicates that a significant number of patients will experience at least some improvement of their symptoms following shunt surgery. Though numerous clinical scoring systems have provided this heterogeneous body of

data, one significant end-point that is seldom reported is the patient-reported outcome (PRO).

PROs are widely used in the clinical literature, often in conditions in which there is no easily quantified primary end-point (106). Given the lack of consensus metrics for measuring objective improvement in the iNPH, PROs

Table 1	
Patient Characteristics at Presentation	
Average age	77.76 years
Sex	
Female	9 (42.86%)
Male	12 (57.14)

could provide insight into the effectiveness of treatment for this disorder.

This analysis examines the experience of patients treated for iNPH at our institution, and will report PROs pertaining to symptom improvement or deterioration following shunt surgery. The primary goal of this analysis is to compare outcomes provided by PROs with the most recent outcomes data reported by reviews of the literature employing traditional clinical scales such as those described in the preceding review (13,16). A secondary objective of this analysis will be to see if there are patient characteristics that significantly correspond to a pattern of response as recorded from PROs.

Methods

Patients

I conducted a retrospective evaluation of patients treated for iNPH with surgical implantation of a CSF diverting shunt between January 2012 and January 2014. All patients' surgeries were performed by the same provider. The diagnosis of iNPH was based on onset of disease in adulthood, progressive worsening of at least one of the three cardinal symptoms of gait disturbance, urinary incontinence, or cognitive impairment, and imaging confirmed communicating ventriculomegaly of unknown etiology. All patients with at least one month of follow-up and documented response to direct questioning about their pre- and post-operative symptom severity were included in the study. In total, 21 patients were included in the final analysis. Relevant patient data can be found in Table 1.

Symptoms at presentation	
Gait	21 (100)
Urinary	19 (90.48)
Cognitive	18 (85.71)
Full triad	17 (80.95)
Response to trial CSF diversion	
Improved	15 (71.43)
Not improved	1 (4.76)
Not performed	5 (23.81)
Duration of symptoms	
< 12 months	9 (42.86)
>12 months	12 (57.14)
Cardiovascular comorbidities	
Hypertension	17 (80.95)
Diabetes mellitus	4 (19.05)
Coronary artery disease	6 (28.57)
Peripheral vascular disease	2 (9.52)
Hyperlipidemia	9 (42.86)
Any	20 (95.24)
Neurologic comorbidities	
Dementia	7 (33.33)
Parkinson's disease	4 (19.05)
History of seizure disorder	2 (9.52)
Tremor	1 (4.76)
Any	9 (42.86)

Evaluation

All patient data were obtained through a search of each patient's electronic medical record.

Patients were evaluated in clinic by the same provider who would later perform shunt surgery. The clinical assessment of the physician with respect to severity of the three cardinal symptoms of gait disturbance, urinary incontinence, and cognitive impairment were recorded in each visit note. Additionally, the patient's assessment of their symptomatology on direct questions about each symptom was recorded in each note. When present, the assessment of the patient's primary health aide (e.g. spouse, visiting nurse) was also recorded. For the purposes of this analysis, a patient was considered to have a symptom at presentation if they endorsed progression of a cardinal symptom over time to the point where it had impacted their quality of life.

Each patient underwent implantation of a right ventriculoperitoneal shunt using a MIETHKE proGAV adjustable, gravitational shunt system. The hospital course and 30-day post-operative period of each patient were assessed for complications. Major complications were considered to be those that led to reoperation, hospital readmission, or deficit which would potentially negate any positive impact conferred by shunting at last follow-up. Minor complications included transient deficits and over- or under-drainage from the shunt system correctable by adjustment of the shunt's settings.

At follow-up, all patients were directly asked to assess their current symptom severity relative to their pre-operative condition. Again, when applicable, the assessments of primary health aides were also recorded. In cases where both the patient's and a health aide's assessments were available, a patient was only scored as improved if both the

patient and the aide considered the patient improved post-operatively. For the purposes of this analysis, only patients who continued to self-report improvement in a symptom domain at their last follow-up were scored as improved.

Based on the pattern of response, patients were divided into a complete-response cohort, for whom all symptom domains were improved by PROs at last follow-up, and an incomplete-response cohort. Significant difference in categorical data between the complete-response cohort and the incomplete-response cohort was examined using a two-tailed Fisher's exact test. As an F-test did not reveal significant difference in variance between the two cohorts, significant difference in continuous data was examined using a standard independent-samples t-test. Significant difference in the rate of response between symptoms was also investigated using a two-tailed Fisher's exact test.

Estimates for frequency of response to shunting reported in the most recent systematic review available for each symptom (13,16) were chosen to represent historical outcomes as measured by traditional clinical scales. Comparison of our cohort data and this historical data was performed using chi-squared analysis.

3.3 Results

All patients reported improvement in at least one symptom domain at last follow-up, and all but five patients reported improvement in all three symptom domains. Of the five patients who experienced no improvement or worsening of at least one patient domain, one patient experienced a worsening of their gait disturbance, one patient experienced no

change in their cognitive impairment, two patients experienced no improvement in their urinary incontinence, and one patient failed to respond in both the urinary and cognitive domains. A summary of the overall pattern of response is available in Table 2.

Table 2		
Response by Symptoms		
	Present pre-operatively	Improved at last follow-up
Symptom		
Gait	21	20 (95.24%)
Urinary	19	16 (84.21)
Cognitive	18	16 (88.89)
Full triad	17	13 (76.47)

There was not a statistically significant difference in response to shunting between patterns of symptomatology at patient presentation.

A comparison of the complete-response cohort to the incomplete-response cohort can be found in Table 3.

Table 3		
Patient Characteristics by Complete or Incomplete Response to Shunting		
	Complete Response (n = 16)	Incomplete Response (n = 5)
Average Age*	76	83.4
Sex		
Female	7 (43.75%)	2 (40%)
Male	9 (56.25)	3 (60)
Symptoms at presentation		
Gait	16 (100)	5 (100)
Urinary	15 (93.75)	4 (80)
Cognitive	13 (81.25)	5 (100)
Response to trial CSF Diversion		
Improved	11 (68.75)	4 (80)
Not improved	1 (6.25)	0 (0)
Not performed	4 (25)	1 (20)
Duration of symptoms		
< 12 months	6 (37.5)	3 (60)
> 12 months	10 (62.5)	4 (40)
Cardiovascular comorbidities		
Hypertension	13 (81.25)	4 (80)
Diabetes mellitus	3 (18.75)	1 (20)
Coronary artery disease	4 (25)	2 (40)
Peripheral vascular disease	1 (12.5)	0 (0)
Hyperlipidemia	7 (43.75)	2 (40)
Any	15 (93.75)	5 (100)
Neurologic comorbidities		
Dementia	5 (31.25)	2 (40)
Parkinson's disease*	1 (6.25)	3 (60)
Any	5 (31.25)	4 (80)
Complications		
Major	2 (12.5)	1 (20)
Minor	4 (25)	1 (20)
Total	6(37.5)	2 (40)
* p-value < 0.05		

The incomplete-response cohort demonstrated significantly higher average age and prevalence of Parkinson's disease than the complete-response cohort. No other significant differences in patient characteristics were demonstrated. With respect to rate of improvement in any symptom domain, a significant difference was seen between our PROs and historical outcomes based on clinical scales. Otherwise, no significant difference was found between our PROs and clinically assessed historical data. These findings are summarized in table 4.

Table 4		
Response Compared to Historical Data		
	% improved - PRO	% improved - historical
Symptom		
Gait	95.24	90
Urinary	84.21	82.5
Cognitive	88.89	80
Any*	100	82
*p-value < 0.05		

Discussion

Patient Selection Rationale and Patient Characteristics

As there is no consensus means of securing a diagnosis of iNPH except for a witnessed response to shunt implantation, and as current evidence suggests that more patients may benefit from earlier shunting, we applied a liberal set of diagnostic criteria, requiring only onset of disease in adulthood, gradual worsening of one of the cardinal symptoms of iNPH, and ventriculomegaly of unknown etiology on neuroimaging. Despite this, our patient population had a higher prevalence of the full clinical triad than what has been reported in previous reviews (10, 13), and most met the criteria for a diagnosis of “probable iNPH” as outlined by Mori *et al* (13).

This inconsistency between our lenient diagnostic criteria and our patient population is likely a result of bias introduced by the referral pattern of our clinic. It is possible that referring physicians did not suspect iNPH until many features of the disease were present.

Though the rate of cardiovascular comorbidity was very high in our patient population, each disease-specific prevalence was not significantly higher than those demonstrated in age-matched population studies (107). This was not the case with neurologic comorbidities; the rates of dementia and Parkinson's disease in our patient population were both approximately five-times greater than those reported for age-matched cohorts in large epidemiologic studies (108,109). These higher rates of neurologic comorbidity may be consistent with previously reported findings of extremely high rates of histopathologic evidence of neurodegenerative disease in patients with iNPH (21,22).

Our patient population largely resembled the population of previous studies of iNPH in so far as they were elderly, gait was the most common symptom at presentation, and the neurologic disease burden was higher than that seen in the general population. It differed from previous iNPH study populations primarily in the frequency with which patients presented with the full clinical triad of gait disturbance, urinary incontinence, and cognitive impairment.

Comparison of Patient-Reported Outcomes to Historical Outcomes

The PROs of this study were responses to a direct question asking the patient to compare their pre- and post-surgical symptom severity. In total, our findings are largely consistent with the historical clinical outcomes data; gait is the most likely symptom to show improvement, while cognitive and urinary symptoms are less responsive. Overall, all three symptoms domains demonstrated a response rate greater than 80% following implantation of a shunt.

Two factors likely contributed to the significant difference in the rate of improvement in any (i.e. at least one) symptom domain demonstrated between this study and the historical data despite the absence of a significant difference in the rate of response for each individual symptom domain. First, it is possible that the insignificant differences in the rate of improvement observed between our data and the historical data with respect to each symptom reached significance when the datasets were combined to tabulate the outcome in the “any” domain. It is also likely that difference in method between the reviews from which the historical data was collected contributed to this result (13,16). Unfortunately, there has not been a single systematic review examining the response of all individual symptoms, which necessitated the compiling of this data from various sources. Likewise, there has been no review on the rate of response to shunting by symptoms at presentation; as such, there was no reliable data available on the historical rate of improvement in the symptoms of patients presenting with the full triad. This would have been useful, as our cohort included a large number of patients with all three cardinal symptoms.

In the absence of a gold-standard metric for assessing outcomes in iNPH, this study demonstrates that PROs obtained from a typical iNPH patient population produce largely similar data on the effectiveness of shunting when compared to the various clinical scales that have been historically employed in the literature. The differences that are observed demonstrate higher rates of symptom improvement, though this is only significant when outcomes from all symptom domains are summed. A larger, prospective study comparing PROs and assessment using a clinical scale would be useful in determining if PROs actually lead to higher reported rates of symptom improvement. If such a difference were to be confirmed, further study would be needed to determine the reasons underlying the patient perception of improvement in the absence of improvement on clinical grading scales.

Comparison of Complete-Response Cohort and Incomplete-Response Cohort

Significant differences in average age and the prevalence of Parkinson's disease were demonstrated between the complete-response cohort and the incomplete-response cohort. The average age of patients in the incomplete-response cohort was more than seven years greater than the average age in the complete-response cohort, and of the four patients in our total patient population with Parkinson's disease, three failed to achieve improvement in all symptom domains. Of note, the symptoms that did not improve in the patients with Parkinson's disease, urinary incontinence and cognitive impairment, are also known to occur in the course of that illness. As such, it is possible that the lack of response to shunting in these patients is the result of their underlying comorbid condition.

Significantly, however, these patients still reported experiencing improvement of their gait dysfunction. This supports previously reported data that even patients with suspected iNPH who also have significant neurologic comorbidity can derive some benefit from shunt implantation (90,91,98,99).

That there is an association between age, comorbid illnesses, and response to shunt surgery in iNPH underscores the fact that careful patient selection based on overall fitness and ability to tolerate surgery is still crucial to obtaining good outcomes. The presence of improvement in at least one symptom in all of our patients, however, indicates that CSF diversion via surgical implantation of a shunt can provide some relief from the symptoms of iNPH even in otherwise significantly ill patients.

Limitations

Limitations of this study include retrospective design, absence of the application of clinical grading scale against which to directly compare PROs in the evaluation of our subjects, and small sample size.

Conclusion

Using patient-reported outcomes to assess patients having undergone shunt surgery for the treatment of iNPH leads to the reporting of similar rates of improvement when compared to historical data obtained through the application of clinical scales. Further study is needed to investigate whether or not PROs lead to higher rates of reported improvement relative to clinical scales, and to elucidate what factors contribute to a

patient's perception of their own improvement. Until a consensus metric for evaluating outcomes in iNPH is established, however, PROs should be considered a viable method of assessing the effectiveness of shunt surgery for the treatment of iNPH.

Appendix 1 – Evidentiary Table

Study	Study Population	Inclusion Criteria	Clinical Scales /Tests Used	Outcome Assessment	Follow-up	Results
Stein and Langfitt (1974)	33 patients with iNPH, 10 with secondary NPH	Progressive Dementia less than 2 years in duration, confirmed ventriculomegaly, normal opening pressure, absence of obstructive etiology	-Stein-Langfitt: Patients rated on a scale from 0 – IV based on overall symptom severity (0 = no symptoms, IV = full custodial care necessary)	Significant improvement defined as at least one point increase in Stein-Langfitt functional score	6-30 months, mean 18 months	24% of patients with INPH showed significant improvement
Black (1980)	62 patients with iNPH	Variable, with minimum criteria of ventriculomegaly, dementia and/or gait disturbances, and normal opening pressure	-Black: Patient outcome scored from “Poor” to “Excellent” based on combination of functional and neurologic outcomes. -Stein-Langfitt	Improvement defined as: Excellent, Good, Fair, or Transient outcome on Black Scale or: one point increase in Stein-Langfitt score	9 weeks to 75 months, mean 36.5 months	46.8% improved by Black scale definition, 33% improved by Stein-Langfitt definition
Raftopoulos, et al. (1996)	23 patients with iNPH	1) Gait disturbances or dementia; 2) Imaging confirmed ventriculomegaly; 3) a mean intraventricular pressure or a lumbar pressure <20 cm H ₂ O; 4) no identifiable cause for hydrocephalus; 5) the ability to walk within one year before the intracranial pressure monitoring; 6) the presence of intracranial pressure waves with an amplitude >9 mm Hg	Gait assessed by equations requiring number of steps, time required, and whether or not assistance is required to walk 10m. Cognition assessed using a battery of psychometric tests including the MMSE.	Results divided into great improvement, moderate improvement, no change, moderate deterioration, or severe deterioration based on an equation comparing pre- and post-procedure results for each symptom assessment test. Shunt response defined as great or	9 days, 2 months, with subsequent annual follow-up	91% of patients continued to show improvement in at least on symptom at last follow-up

				moderate improvement.		
Krauss, et al. (1996)	41 patients with iNPH	Gait disturbance, imaging confirmed ventriculomegaly, improvement of gait disturbances with CSF removal	Gait, cognitive, and urinary symptoms scored from 0-3 (0 = no symptoms, 3 = severe symptoms). Improvement in each symptom following shunting scored from 0-2 (0 = no improvement, 2 = significant improvement) -Krauss Improvement Index (KII): (sum of improvement scores)/2n, where "n" is the number of cardinal symptoms manifest at presentation	Shunt response was defined as a KII > 0 at last follow-up.	3-59 months, average follow-up 16 months	90% of patients with gait disturbance, 88% of patients with cognitive impairment, and 76% of patients with urinary symptoms showed improvement at last follow-up.
Boon, et al. (1998)	85 patients with iNPH, 11 with secondary NPH	Gradually developing gait disturbance effecting both legs, mild to moderate cognitive impairment without aphasia, mRS of at least 2, imaging-confirmed communicating hydrocephalus,	NPH scale (sum of dementia and gait scales), Modified Mini Mental State Exam, mRS	Categorized as none, moderate, marked, or excellent based on % improvement in NPH score <i>or</i> improvement in mRS	1, 3, 6, 9, and 12 months	74% of patients implanted with low-pressure shunts, and 53% of patients implanted with medium high-pressure shunts showed some improvement, with the mRS definition providing more statistically significant findings
Malm, et al. (2000)	42 patients with iNPH	Imaging confirmed ventriculomegaly without significant leucoaraiosis, gait disturbances	MMSE, Barthel Index, video recording of ambulation	Response to shunting defined as MMSE score greater than or equal to 25 <i>or</i> an increase of at least two points in MMSE score <i>or</i>	3, 9, 18, and 36 months	Mental status and gait responded to shunting in 69% and 67.5% of patients at 3 months, and 28% and 26% at 36 months, respectively. 75% of patients were living independently at 3

				clinician assessment of improved ambulation. Independent living defined as Barthel Index > 65		months, versus 28 % at 36 months.
Mori (2001)	120 patients with iNPH	Imaging confirmed ventriculomegaly and presence of full clinical triad of gait disturbances, cognitive impairment, and urinary incontinence	iNPH grading scale established by the Research Committee on Intractable Hydrocephalus (Japan) – calculated from sum score from 0-4 for each cardinal symptom (0 = no symptoms, 4 = worst symptoms)	Response to shunting defined as improvement by at least on point on iNPH scale	3 and 36 months	80% of patients showed improvement at 3 months, and 73.3% had sustained improvement at 36 months. Gait symptoms were more likely to improve than dementia or urinary symptoms (79.2% v. 20.8%, respectively, at 3 months)
Kiefer, et al. (2002)	91 patients with iNPH	Variable; based on clinical presentation and CSF dynamic parameters	-Kiefer Index (KI): gait, cognitive, and urinary symptoms scored from 0-6, headache from 0-4, and dizziness from 0-2. Scores summed to provide Kiefer index (high = more symptomatic disease) -Recovery Index (RI): $[(\text{preop KI} - \text{postop KI}) \times 10] / (\text{preop KI})$	Response to shunting defined as: -Non-responders (RI 0-1) -Moderate response (RI 2-4) -Good response (RI 5-7) -Very good response (RI > 7)	6 to 60 months, average follow-up 26 months	>65% of patients had good or very good recovery at last follow-up. 88% of patients were shunt responders.
Poca, et al. (2004)	43 patients with iNPH	Imaging confirmed ventriculomegaly, and at least one of the following symptoms: gait disturbance, cognitive deficits, treatment refractory Parkinsonism, or sphincter incontinence.	iNPH scale calculated from sum of score from 1-5 for each cardinal symptom (1 = severe symptoms, 5 = no symptoms). Stein-Langfitt. Activities of Daily Living Scale. Informant Questionnaire	Improvement categorized as: -None -Mild (improvement of one point on NPH scale) -Moderate (improvement of	6 months	86% of patients showed some improvement. Gait, incontinence, and cognitive symptoms experienced improvement rates of 85%, 86%, and 40%, respectively. Neuropsychological testing and MMSE did not

			on Cognitive Decline in the Elderly	two or more points on NPH scale)		show statistically significant difference pre- and post- procedure.
Poca, et al. (2005)	12 patients with iNPH and negative prognostic factors	Same as Poca, et al.(2004), plus age > 65, symptom duration > 12 months, cortical atrophy, and MMSE < 24	Same as above	Improvement categorized as: -None -Mild (improvement of one point on scale) -Moderate (improvement of two or more points on scale)	6 months	92% of patients experienced some improvement. Gait, incontinence, and cognitive symptoms experienced improvement rates of 92%, 92%, and 33%, respectively. Neuropsychological testing and MMSE did not show statistically significant difference pre- and post- procedure.
McGirt, et al. (2005)	132 patients with iNPH	Confirmed ventriculomegaly, at least two of the symptoms of gait disturbance, cognitive deficit, or urinary incontinence, no obvious etiology of their hydrocephalus, A- or B-waves on continuous CSF pressure monitoring, and improvement with 3-day lumbar drain trial	MMSE, patient or care provider reported quality of life	Improvement in symptoms assessed based on patient-reported improvement. Cognitive symptoms additionally considered improved with > 3 point increase in MMSE. Response to shunting scored as improvement in at least one symptom.	1, 3, and 6 months with subsequent annual follow-up, mean follow-up of 18 months.	75% of patients showed improvement in at least one symptom and 46% had improvement in all of their symptoms at the study's conclusion. Gait disturbance was the most likely symptom to improve
Eide, et al. (2006)	39 patients with iNPH	Not specified	iNPH scale calculated from sum of score from 1-5 for each cardinal symptom (1 = severe symptoms, 5 = no	Improvement categorized as: -Very Significant (> 5 point improvement on	12 months	69% of patients showed some improvement at 12 months. 31% showed very significant improvement, and 15% showed

			symptoms).	iNPH scale) -Significant (3-4 point improvement on iNPH scale -Slight Improvement (1-2 point improvement on iNPH scale) -Non-responders		significant improvement.
Kahlon, et al. (2007)	46 patients with iNPH, 8 with secondary NPH	Imaging confirmed ventriculomegaly, at least one of symptoms of gait disturbance, cognitive impairment, or urinary incontinence, and <i>either</i> positive lumbar infusion test of CSF tap test	Walk time, step number reaction time, memory, identical forms tests, and Barthel index	Authors report % change in scores of pre- and post-operative tests	6 months (all patients) and 5 years (23 patients)	More than 80% of patients showed objective improvement and 96% reported subjective improvement at six months. 43% of patients showed some objective improvement and 56% reported subjective improvement at 5 years
Kubo, et al. (2007)	38 patient with iNPH evaluated to validate new iNPH scale. 14 eventually shunted.	Age > 60 years, at least one of the symptoms of gait disturbance, cognitive impairment, or urinary incontinence, imaging confirmed ventriculomegaly, absence of known etiology of hydrocephalus, and normal opening pressure on lumbar puncture. Decision to shunt based on individual surgeon's opinion.	iNPH grading scale calculated as sum of score from 0-4 for each cardinal symptom (0 = no symptoms, 4 = worst symptoms). MMSE, Frontal Assessment Battery, Gait Status Scale, Timed up-and-go, International Consultation on Incontinence Questionnaire – Short Form	Quantified change in iNPH scale presented in results	1 to 12 months	79% of shunted patients showed at least one point of improvement on the iNPH grading scale
Pujari, et al. (2008)	55 patients with iNPH	See: McGirt (2005)	MMSE, Tinetti gait score, patient or care provider	See: McGirt (2005)	1, 3, and 6 months, with	71% of patients reported improvement in all

			reported quality of life		annual follow-up thereafter. Patients followed for a minimum of 3 years, maximum of 7 years.	symptoms at 3 years following shunt surgery. 80% of patients still followed at 7 years continued to report improvement of all symptoms relative to pre-surgical baseline.
Kiefer, et al. (2010)	75 patients with iNPH, 50 patients with "non-iNPH"	Presentation with at least two of the symptoms of gait disturbance, cognitive impairment, or urinary incontinence, and imaging confirmed ventriculomegaly	-Kiefer Index (KI) -Recover Index (RI) -Comorbidity Index (CMI): between 1-3 points assigned for comorbidities in each of the following categories: peripheral vascular disease/vascular risk factors, cerebrovascular disease, electrical/structural heart disease, and other neurologic disease	Response to shunting defined at RI > 3 at final follow-up	2-3 months, 12 months, then annually. Average follow-up of 5.1 years	iNPH patients with CMI 0-3 had >80% response rate. When controlled for age and CMI, there was no statistically significant difference in the response rate between iNPH and non-iNPH. Patients with iNPH were ten-fold more likely to have an older age and a higher CMI at presentation than patients with non-iNPH.
Mirzayan, et al. (2010)	51 patients with iNPH	Presence of gait disturbance, imaging confirmed ventriculomegaly with flattening of the parasagittal, frontoparietal sulci, and improvement of gait with CSF drainage	Krauss Improvement Index	KII reported in results	Divided into "short term" and "long term" follow-up. -Short term: avg. 18.8 months. -Long term: avg. 80.9 months	Average long-term KII for gait, cognitive, and urinary symptoms were .75, .67, and .67, respectively.
Hashimoto, et al. (2010)	100 patients with iNPH	Age between 60 and 85, at least one of the symptoms of gait disturbance, cognitive	mRS, Kubo's iNPH grading scale, Timed up-and-go, MMSE	Response to shunting defined as at least one point of improvement on	12 months	80% of patients responded to shunting

		impairment, or urinary incontinence, imaging confirmed ventriculomegaly, absence of known etiology of hydrocephalus, and opening pressure < 20cm H2O on LP		mRS at one year		
Tisell, et al. (2011)	14 patients with iNPH and Binswanger's disease	Confirmed ventriculomegaly, "symptoms and signs of iNPH", and Wahlund score 2 or 3 white matter changes	Seven psychometric tests (Bingley, Identical Forms, Reaction Time, Grooved Pegboard, RAVLT, Tracks, Stroop Color Naming) and six motor tasks (time to sit upright from lying down, time to walk 10 m, time to climb up and down six stairs, no. of steps to turn 180, no. of steps to walk 3 m backwards)	Response to shunting measured as change in mean of motor and psychometric tests	3 and 6 months	22% overall improvement in aggregate average scores for all 14 patients at 6 months
Klinge, et al. (2012)	115 patients with iNPH	Split patients into "typical" or "questionable" iNPH. -Typical: 1) Gradual onset of gait disturbance effecting tandem walk, turning, and stride length; 2) mild to moderate (MMSE score greater than or equal to 21) cognitive impairment presenting together with or after presentation of gait symptoms; 3) MRI	mRS, -Hellstrom's iNPH scale: The domains of gait impairment, cognitive ability, balance, and urinary incontinence are each given a score from 0-100 based on a combination of ordinal clinical scales or objective tests unique to each symptom. The iNPH score is then calculated by the equation [2(gait)+(cognitive)+(bala	Response to shunting defined as improvement in mRS of at least one point <i>or</i> improvement of at least 5 points on Hellstrom's iNPH scale	12 months	64% and 84% of patients were improved at one year by mRS and Hellstrom's iNPH scale criteria, respectively. 82% of patients were living independently at one year compared to 53% before surgery.

		findings of quadriventricular enlargement with little or no leucoaraiosis. -Questionable: 1) atypical gait disturbances; 2) cognitive impairment including aphasia, apraxia, or agnosia, <i>or</i> MMSE score < 21; 3) MRI with ventriculomegaly and cortical atrophy, also including either mild to severe leucoaraiosis or single area of infarct	nce)+(urinary)]/5(or total number of scores available)			
Andren, et al. (2014)	33 patients with iNPH waiting at least 6 months between diagnosis and shunt surgery, and 69 patients waiting no more than 3 months between diagnosis and shunt surgery	“Possible” or “probable” iNPH as per criteria set forth in most recent international guidelines (10)	Hellstrom’s iNPH scale	Improvement of at least 5 points on Hellostrom’s iNPH scale	3 months	Significant improvement following shunting was demonstrated in all symptoms domains in each group. There was a significant difference in the degree of improvement between the delayed shunting cohort and the early shunting cohort, with the early shunting cohort having a greater degree of improvement in all domains except for incontinence and MMSE, for which there was no significant difference between the groups.

References

1. Hakim, S., Adams, R.D. 1965. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J Neurol Sci.* 2:307–327.
2. Adams, R.D., Fisher, C.M., Hakim, S., Ojemann, R.G., Sweet, W.H. 1965. Symptomatic occult hydrocephalus with 'normal' cerebrospinal fluid pressure: A treatable syndrome. *N Engl J Med.* 273:117-126.
3. Stein, S.C., Langfitt, T.W. 1974. Normal pressure hydrocephalus. Predicting the results of cerebrospinal fluid shunting. *J Neurosurg.* 41:463–469.
4. Black, P.M. 1980. Idiopathic normal pressure hydrocephalus: Results of shunting in 62 patients. *Journal of Neurosurgery.* 52:371–377.
5. Petersen, R.C., Mokri, B., Laws, E.R. Jr. 1985. Surgical treatment of idiopathic hydrocephalus in elderly patients. *Neurology.* 35:307–311.
6. Vanneste, J., Augustijn, P., Dirven, C., Tan, W.F., Goedhart, Z.D. 1992. Shunting normalpressure hydrocephalus: Do the benefits outweigh the risks? A multicenter study and literature review. *Neurology.* 42:54–59.
7. Boon, A.J., Tans, J.T., Delwel, E.J., Crook, T. 1997. Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *J Neurosurg.* 87:687–693.
8. McGirt, M.J., Woodworth, G., Coon, A.L., Thomas, G., Williams, M.A., *et al.* 2005. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. *Neurosurgery.* 57:699–705.
9. Silverberg, G.D., Mayo, M., Saul, T., Fellmann, J., Carvalho, J., *et al.* Continuous CSF drainage in AD: results of a double-blind, randomized, placebo-controlled study. *Neurology.* 71:202-209.
10. Relkin, N., Marmarou, A., Klinge, P., Bergsneider, M., Black, P.M. 2005. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery.* 57:S2-4-S2-16.
11. Marmarou, A., Bergsneider, M., Relkin, N., Klinge, P., Black, P.M. 2005. INPH guidelines, part I: development of guidelines for idiopathic normal-pressure hydrocephalus: Introduction. *Neurosurgery.* 57:S2-1–S2-3.
12. Klinge, P., Marmarou, A., Bergsneider, M., Relkin, N., Black, P.M. 2005. INPH guidelines, part V: outcome of shunting in idiopathic normalpressure hydrocephalus and the value of outcome assessment in shunted patients. *Neurosurgery.* 57:S2-40–S2-52.
13. Mori, E., Ishikawa, M., Kato, T., Kazui, H., Miyake, H., *et al.* 2012. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. *Neurol Med Chir (Tokyo).* 52:775–809.
14. Marmarou, A., Black, P., Bergsneider, M., Klinge, P., Relkin, N. 2005. International NPH Consultant Group. Guidelines for management of idiopathic normal pressure hydrocephalus: progress to date. *Acta Neurochir Suppl.* 95:237–240.
15. McGirr, A., Mohammed, S., Kurlan, R., Cusimano, M. 2013. Clinical equipoise in idiopathic normal pressure hydrocephalus: A survey of physicians on the need for randomized controlled trials assessing the efficacy of cerebrospinal fluid diversion. *J Neurol Sci.* In press.
16. Toma, A., Papadopoulos, M., Stapleton, S., Kitchen, N., Watkins, L. 2013. Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. *Acta Neuro.* 115:1977-1980.
17. Trenkwalder, C., Schwarz, J., Gebhard, J., Ruland, D., Trenkwalder, P., *et al.* 1995. Starnberg trial on epidemiology of Parkinsonism and hypertension in the elderly. Prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. *Arch Neurol.* 52:1017-1022.
18. Brean, A., Eide, P.K. 2008. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. *Acta Neurol Scand.* 118:48-53.
19. Tanaka, N., Yamaguchi, S., Ishikawa, H., Ishii, H., Meguro, K. 2009. Prevalence of possible idiopathic normal pressure hydrocephalus in Japan: The Osaki-Tajiri project. *Neuroepidemiology.* 32:171-175.

20. Marmarou, A., Young, H.F., Aygok, G.A. 2007. Estimated incidence of normal pressure hydrocephalus and shunt outcome in patients residing in assisted-living and extended-care facilities. *Neurosurg Focus*. 22:E1.
21. Bech-Azeddine, R., Høgh, P., Juhler, M., Gjerris, F., Waldemar, G. 2007. Idiopathic normal-pressure hydrocephalus: clinical comorbidity correlated with cerebral biopsy findings and outcome of cerebrospinal fluid shunting. *J Neurol Neurosurg Psychiatry*. 78:157–61.
22. Golomb, J., Wisoff, J., Miller, D.C., Boksay, I., Kluger, A., *et al.* 2000. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. *J Neurol Neurosurg Psychiatry*. 68:778–781.
23. Kiefer, M., Unterberg, A. 2012. The differential diagnosis and treatment of normal-pressure hydrocephalus. *Dtsch Arztebl Int*. 109:15–26.
24. Silverberg, G.D. 2004. Normal pressure hydrocephalus (NPH): ischaemia, CSF stagnation or both. *Brain*. 127:947-948.
25. Malm, J., Eklund, A. 2006. Idiopathic normal pressure hydrocephalus. *Pract Neurol*. 6:14-27.
26. Ojemann, R.G., Fisher, C.M., Adams, R.D., Sweet, W.H., New, P.F. 1969. Further experiences with the syndrome of normal pressure hydrocephalus. *J Neurosurg*. 31:279-294.
27. Shprecher, D., Schwalb, J., Kurlan, R. 2008. Normal pressure hydrocephalus: diagnosis and treatment. *Curr Neurol Neurosci Rep*. 8:371–376.
28. Hashimoto, M., Ishikawa, M., Mori, E., Kuwana, N., Study of INPH on neurological improvement (SINPHONI). 2010. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. *Cerebrospinal Fluid Res*. 7:18.
29. Williams, M.A., Thomas, G., de Lateur, B., Imteyaz, H., Rose, J.G., *et al.* 2008. Objective assessment of gait in normal-pressure hydrocephalus. *Am J Phys Med Rehabil*. 87:39–45.
30. Chaudhry, P., Kharkar, S., Heidler-Gary, J., Hillis, A.E., Newhart, M., *et al.* 2007. Characteristics and reversibility of dementia in normal pressure hydrocephalus. *Behav Neurol*. 18:149–158.
31. Sakakibara, R., Kanda, T., Sekido, T., Uchiyama, T., Awa, Y., *et al.* 2008. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. *Neurol Urodyn*. 27:507-510.
32. Malm, J., Kristensen, B., Karlsson, T., Fagerlund, M., Elfverson, J., *et al.* 1995. The predictive value of cerebrospinal fluid dynamic tests in patients with the idiopathic adult hydrocephalus syndrome. *Arch Neurol*. 52:783–789.
33. Evans, W.A. 1942. An encephalographic ratio for estimating ventricular and cerebral atrophy. *Arch Neurol Psychiatry*. 147:931–937.
34. Borgesen, S.E., Gjerris, F. 1982. The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. *Brain*. 105:65–86.
35. Golomb, J., de Leon, M.J., George, A.E., Kluger, A., Convit, A., Rusinek, H., *et al.* 1994. Hippocampal atrophy correlates with severe cognitive impairment in elderly patients with suspected normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry*. 57:590–593.
36. Benzel, E.C., Pelletier, A.L., Levy, P.G. 1990. Communicating hydrocephalus in adults: prediction of outcome after ventricular shunting procedures. *Neurosurgery*. 26:655–660.
37. Tullberg, M., Jensen, C., Ekholm, S., Wikkelsø, C. 2001. Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. *AJNR Am J Neuroradiol*. 22:1665–1673.
38. Kitagaki, H., Mori, E., Ishii, K., Yamaji, S., Hirono, N., *et al.* 1998. CSF spaces in idiopathic normal pressure hydrocephalus: morphology and volumetry. *AJNR Am J Neuroradiol*. 19:1277-84.
39. Ishii, K., Kanda, T., Harada, A., Miyamoto, N., Kawaguchi, T., *et al.* 2008. Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. *Eur Radiol*. 18:2678-83.
40. Virhammar, J., Laurell, K., Cesarini, K.G., Larsson, E.M. 2014. The callosal angle measured on MRI as a predictor of outcome in idiopathic normal-pressure hydrocephalus. *J Neurosurg*. 120:178-84.
41. Palm, W.M., Walchenbach, R., Bruinsma, B., Admiraal-Behloul, F., Middelkoop, H.A., *et al.* 2006. Intracranial compartment volumes in normal pressure hydrocephalus: volumetric assessment versus outcome. *AJNR Am J Neuroradiol*. 27:76–79.

42. Hashimoto, M., Ishikawa, M., Mori, E., Kuwana, N. 2010. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. *Cerebrospinal Fluid Res.* 7:18.
43. Lee, W.J., Wang, S.J., Hsu, L.C., Lirng, J.F., Wu, C.H., *et al.* 2010. Brain MRI as a predictor of CSF tap test response in patients with idiopathic normal pressure hydrocephalus. *J Neurol.* 257:1675-81.
44. Tullberg, M., Jensen, C., Ekholm, S., Wikkelso, C. 2001. Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. *AJNR Am J Neuroradiol.* 22:1665–1673.
45. Bradley, W.G. Jr., Whittemore, A.R., Kortman, K.E., Watanabe, A.S., Homyak, M., *et al.* 1991. Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus. *Radiology.* 178:459–466.
46. Bradley, W.G. Jr., Scalzo, D., Queralt, J., Nitz, W.N., Atkinson, D.J., *et al.* 1996. Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. *Radiology.* 198:523–529.
47. Dixon, G.R., Friedman, J.A., Luetmer, P.H., Quast, L.M., McClelland, R.L., *et al.* 2002. Use of cerebrospinal fluid flow rates measured by phase-contrast MR to predict outcome of ventriculoperitoneal shunting for idiopathic normal-pressure hydrocephalus. *Mayo Clin Proc.* 77:509–514.
48. Bateman, G.A., Levi, C.R., Schofield, P., Wang, Y., Lovett, E.C. 2005. The pathophysiology of the aqueduct stroke volume in normal pressure hydrocephalus: can co-morbidity with other forms of dementia be excluded? *Neuroradiology.* 47:741–748.
49. Forner Giner, J., Sanz-Requena, R., Flórez, N., Alberich-Bayarri, A., García-Martí, G., *et al.* 2013. Quantitative phase-contrast MRI study of cerebrospinal fluid flow: A method for identifying patients with normal-pressure hydrocephalus. *Neurologia.* In press.
50. Tarnaris, A., Kitchen, N.D., Watkins, L.D. 2009. Noninvasive biomarkers in normal pressure hydrocephalus: evidence for the role of neuroimaging. *J Neurosurg.* 110:837-51.
51. Jagust, W.J., Friedland, R.P., Budinger, T.F. 1985. Positron emission tomography with [¹⁸F]fluorodeoxyglucose differentiates normal pressure hydrocephalus from Alzheimer-type dementia. *J Neurol Neurosurg Psychiatry.* 48:1091–1096.
52. Momjian, S., Owler, B.K., Czosnyka, Z., Czosnyka, M., Pena, A., *et al.* 2004. Pattern of white matter regional cerebral blood flow and autoregulation in normal pressure hydrocephalus. *Brain.* 127:965–972.
53. Owler, B.K., Pena, A., Momjian, S., Czosnyka, Z., Czosnyka, M., *et al.* 2004 Changes in cerebral blood flow during cerebrospinal fluid pressure manipulation in patients with normal pressure hydrocephalus: a methodological study. *J Cereb Blood Flow Metab.* 24:579–587.
54. Klinge, P.M., Brooks, D.J., Samii, A., Weckesser, E., van den Hoff, J., *et al.* 2008. Correlates of local cerebral blood flow (CBF) in normal pressure hydrocephalus patients before and after shunting--A retrospective analysis of [(15)O]H(2)O PET-CBF studies in 65 patients. *Clin Neurol Neurosurg.* 110:369-75.
55. Calcagni, M.L., Taralli, S., Mangiola, A., Indovina, L., Lavallo, M., *et al.* 2013. Regional cerebral metabolic rate of glucose evaluation and clinical assessment in patients with idiopathic normal-pressure hydrocephalus before and after ventricular shunt placement: a prospective analysis. *Clin Nucl Med.* 38:426-31.
56. Graff-Radford, N.R., Rezai, K., Godersky, J.C., Eslinger, P., Damasio, H., *et al.* 1987. Regional cerebral blood flow in normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry.* 50:1589-96.
57. Graff-Radford, N.R., Godersky, J.C., Jones, M.P. 1989. Variables predicting surgical outcome in symptomatic hydrocephalus in the elderly. *Neurology.* 39:1601-4.
58. Chang, C.C., Kuwana, N., Ito, S., Ikegami, T. 1999. Prediction of effectiveness of shunting in patients with normal pressure hydrocephalus by cerebral blood flow measurement and computed tomography cisternography. *Neurol Med Chir (Tokyo).* (12):841-5; discussion 845-6.
59. Ishii, K., Hashimoto, M., Hayashida, K., Hashikawa, K., Chang, C.C., *et al.* 2011. A multicenter brain perfusion SPECT study evaluating idiopathic normal-pressure hydrocephalus on neurological improvement. *Dement Geriatr Cogn Disord.* 32:1-10

60. Kazui, H., Mori, E., Ohkawa, S., Okada, T., Kondo, T., *et al.* 2013. Predictors of the disappearance of triad symptoms in patients with idiopathic normal pressure hydrocephalus after shunt surgery. *J Neurol Sci.* 328:64-9.
61. Ziegelitz, D., Starck, G., Kristiansen, D., Jakobsson, M., Hultenmo, M., *et al.* 2013. Cerebral perfusion measured by dynamic susceptibility contrast MRI is reduced in patients with idiopathic normal pressure hydrocephalus. *J Magn Reson Imaging.* Epub ahead of print
62. Oowler, B.K., Pickard, J.D. 2001. Normal pressure hydrocephalus and cerebral blood flow: a review. *Acta Neurol Scand.* 104:325-342.
63. Kim, M.J., Seo, S.W., Lee, K.M., Kim, S.T., Lee, J.I., *et al.* 2011. Differential diagnosis of idiopathic normal pressure hydrocephalus from other dementias using diffusion tensor imaging. *AJNR Am J Neuroradiol.* 32(8):1496-503.
64. Koyama, T., Marumoto, K., Domen, K., Miyake, H. 2013. White matter characteristics of idiopathic normal pressure hydrocephalus: a diffusion tensor tract-based spatial statistic study. *Neurol Med Chir (Tokyo).* 53(9):601-8.
65. Hattinen, E., Jurcoane, A., Melber, J., Blasel, S., Zanella, F.E., *et al.* 2010. Diffusion tensor imaging in patients with adult chronic idiopathic hydrocephalus. *Neurosurgery.* 66:917-24.
66. Hattori, T., Sato, R., Aoki, S., Yuasa, T., Mizusawa, H. 2012. Different patterns of fornix damage in idiopathic normal pressure hydrocephalus and Alzheimer disease. *AJNR Am J Neuroradiol.* 33(2):274-9.
67. Ivkovic, M., Liu, B., Ahmed, F., Moore, D., Huang, C., *et al.* 2013. Differential diagnosis of normal pressure hydrocephalus by MRI mean diffusivity histogram analysis. *AJNR Am J Neuroradiol.* 34(6):1168-74
68. Gideon, P., Thomsen, C., Gjerris, F., Sørensen, P.S., Henriksen, O. 1994. Increased self-diffusion of brain water in hydrocephalus measured by MR imaging. *Acta Radiol.* 35:514-519.
69. Corkill, R.G., Garnett, M.R., Blamire, A.M., Rajagopalan, B., Cadoux-Hudson, T.A., *et al.* 2003. Multi-modal MRI in normal pressure hydrocephalus identifies pre-operative haemodynamic and diffusion coefficient changes in normal appearing white matter correlating with surgical outcome. *Clin Neurol Neurosurg.* 105:193-202.
70. Ohno, N., Miyati, T., Mase, M., Osawa, T., Kan, H., *et al.* 2011. Idiopathic normal-pressure hydrocephalus: temporal changes in ADC during cardiac cycle. *Radiology.* 261(2):560-5.
71. Osawa, T., Mase, M., Miyati, T., Kan, H., Demura, K., Kasai, H., *et al.* 2012. Delta-ADC (apparent diffusion coefficient) analysis in patients with idiopathic normal pressure hydrocephalus. *Acta Neurochir Suppl.* 114:197-200.
72. Nooijen, P.T., Schoonderwaldt, H.C., Wevers, R.A., Hommes, O.R., Lamers, K.J. 1997. Neuron-specific enolase, S-100 protein, myelin basic protein and lactate in CSF in dementia. *Dement Geriatr Cogn Disord.* 8:169-173.
73. Kizu, O., Yamada, K., Nishimura, T. 2001. Proton chemical shift imaging in normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 22:1659-1664.
74. Algin, O., Hakyemez, B., Parlak, M. 2010. Proton MR Spectroscopy and white matter hyperintensities in idiopathic normal pressure hydrocephalus and other dementias. *Br J Radiol.* 83(993):747-52.
75. Lundin, F., Tisell, A., Dahlqvist-Leinhard, O., Tullberg, M., Wikkelsö, C., *et al.* 2011. Reduced thalamic N-acetylaspartate in idiopathic normal pressure hydrocephalus: a controlled 1H-magnetic resonance spectroscopy study of frontal deep white matter and the thalamus using absolute quantification. *J Neurol Neurosurg Psychiatry.* 82(7):772-8.
76. Mitchell, P., Mathew, B. 1999. Third ventriculostomy in normal pressure hydrocephalus. *Br J Neurosurg.* 13:382-385.
77. Gangemi, M., Maiuri, F., Naddeo, M., Godano, U., Mascari, C., *et al.* 2008. Endoscopic third ventriculostomy in idiopathic normal pressure hydrocephalus: an Italian multicenter study. *Neurosurgery.* 63:62-67.
78. Hailong, F., Guangfu, H., Haibin, T., Hong, P., Yong, C., *et al.* 2008. Endoscopic third ventriculostomy in the management of communicating hydrocephalus: a preliminary study. *J Neurosurg.* 109:923-930.
79. Paidakakos, N., Borgarello, S., Naddeo, M. 2012. Indications for endoscopic third ventriculostomy in normal pressure hydrocephalus. *Acta Neurochir Suppl.* 113:123-127.

80. Chan, A.K., McGovern, R.A., Zacharia, B.E., Mikell, C.B., Bruce, S.S., *et al.* 2013. Inferior short-term safety profile of endoscopic third ventriculostomy as compared to ventriculoperitoneal shunt placement for idiopathic normal pressure hydrocephalus: A population-based study. *Neurosurgery*. In press.
81. Pinto, F.C., Saad, D., Oliveira, M.F., Pereira, R.M., Miranda, F.L., *et al.* 2013. Role of endoscopic third ventriculostomy and ventriculoperitoneal shunt in idiopathic normal pressure hydrocephalus: preliminary results of a randomized clinical trial. *Neurosurgery*. 72:845-853.
82. Toma, A.K., Papadopoulos, M.C., Stapleton, S., Kitchen, N.D., Watkins, L.D. Conservative versus surgical management of idiopathic normal pressure hydrocephalus: a prospective double-blind randomized controlled trial: study protocol. *Acta Neurochir Suppl*. 113:21-23.
83. Toma, A.K., Stapleton, S., Papadopoulos, M.C., Kitchen, N.D., Watkins, L.D. 2010. Natural history of idiopathic normal-pressure hydrocephalus. *Neurosurg Rev*. 2011-2019.
84. Raftopoulos, C., Massager, N., Baleriaux, D., Deleval, J., Clarysse, S., *et al.* 1996. Prospective Analysis by Computed Tomography and Long-term Outcome of 23 Adult Patients with Chronic Idiopathic Hydrocephalus. *Neurosurgery*. 38:51-59.
85. Krauss, J.K., Droste, D.W., Vach, W., Regel, J.P., Orszagh, M., *et al.* 1996. Cerebrospinal Fluid Shunting in Idiopathic Normal-Pressure Hydrocephalus of the Elderly: Effect of Periventricular and Deep White Matter Lesions. *Neurosurgery*. 39:292-300.
86. Boon, A.J., Tans, J.T., Delwel, E.J., Egeler-Peerdeman, S.M., Hanlo, P.W., *et al.* Dutch Normal-Pressure Hydrocephalus Study: randomized comparison of low- and medium-pressure shunts. *J Neurosurg*. 88:490-495.
87. Malm, J., Kristensen, B., Stegmayr, B., Fagerlund, M., Koskinen, L.O. 2000. Three-year survival and functional outcome of patients with idiopathic adult hydrocephalus syndrome. *Neurology*. 55:576-578.
88. Mori, K. 2001. Management of idiopathic normal-pressure hydrocephalus: a multiinstitutional study conducted in Japan. *J Neurosurg*. 95:970-973.
89. Kiefer, M., Eymann, R., Meier, U. 2002. Five Years Experience with Gravitational Shunts in Chronic Hydrocephalus of Adults. *Acta Neurochir*. 144:755-767.
90. Poca, M.A., Mataró, M., Del Mar Matarín, M., Arian, F., Junqué, C., *et al.* 2004. Is the placement of shunts in patients with idiopathic normal-pressure hydrocephalus worth the risk? Results of a study based on continuous monitoring of intracranial pressure. *J Neurosurg*. 100:855-866.
91. Poca, M.A., Mataró, M., Matarín, M., Arian, F., Junqué, C., *et al.* 2005. Good outcome in patients with normal-pressure hydrocephalus and factors indicating poor prognosis. *J Neurosurg*. 103:455-463.
92. Eide, P.K. 2006. Intracranial pressure parameters in idiopathic normal pressure hydrocephalus patients treated with ventriculo-peritoneal shunts. *Acta Neurochir*. 148:21-29.
93. Kahlon, B., Sjunnesson, J., Rehncrona, S. 2007. Long-term outcome in patients with suspected normal pressure hydrocephalus. *Neurosurgery*. 60(2):327-332.
94. Kubo, Y., Kazui, H., Yoshida, T., Kito, Y., Kimura, N., *et al.* 2008. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. *Dement Geriatr Cogn Disord*. 25:37-45.
95. Pujari, S., Kharkar, S., Metellus, P., Shuck, J., Williams, M.A., *et al.* 2008. Normal pressure hydrocephalus: long-term outcome after shunt surgery. *J Neurol Neurosurg Psychiatry*. 79:1282-1286.
96. Kiefer, M., Meier, U., Eymann, R. 2010. Does idiopathic normal pressure hydrocephalus always mean a poor prognosis? *Acta Neurochir Suppl*. 106:101-106.
97. Mirzayan, M.J., Luetjens, G., Borremans, J.J., Regel, J.P., Krauss, J.K. 2001. Extended long-term (> 5 years) outcome of cerebrospinal fluid shunting in idiopathic normal pressure hydrocephalus. *Neurosurgery*. 67:295-301.
98. Tisell, M., Tullberg, M., Hellström, P., Edsbacke, M., Högfeldt, M., *et al.* 2011. Shunt surgery in patients with hydrocephalus and white matter changes. *J Neurosurg*. 144:1432-1438.
99. Klinge, P., Hellstrom, P., Tans, J., Wikkelsø, C. 2012. One-year outcome in the European multicentre study on iNPH. *Acta Neurol Scand*. 126:145-153.
100. Lemcke, J., Meier, U., Müller, C., Fritsch, M.J., Kehler, U., *et al.* 2013. Safety and efficacy of gravitational shunt valves in patients with idiopathic normal pressure hydrocephalus: a

- pragmatic, randomised, open label, multicentre trial (SVASONA). *J Neurol Neurosurg Psychiatry*. 84:850-857.
101. Woodford, H.J., George, J. 2007. Cognitive assessment in the elderly: a review of clinical methods. *QJM*, 100:469-484.
 102. Hellstrom, P., Klinge, P., Tans, J., Wikkelsø, C. 2012. A new scale for assessment of severity and outcome in iNPH. *Acta Neurol Scand*. 126:229-237.
 103. Hebb, A.O., Cusimano, M.D. 2001. Idiopathic Normal Pressure Hydrocephalus: A Systematic Review of Diagnosis and Outcome. *Neurosurgery*. 49:1166-1184.
 104. Stein, S.C., Burnett, M.G., Sonnad, S.S. Shunts in normal-pressure hydrocephalus: do we place too many or too few? *J Neurosurg*. 105:815-822.
 105. Andren, K., Wikkelsø, C., Tisell, M., Hellstrom, P. 2014. Natural course of idiopathic normal pressure hydrocephalus. *Neurosurgery*. In press.
 106. Eton, D.T., Beebe, T.J., Hagan, P.T., Halyard, M.Y., Montori, V.M., *et al*. 2014. Harmonizing and consolidating the measurement of patient-reported information at health care institutions: a position statement of the Mayo Clinic. *Patient Relat Outcome Meas*. 5:7-15.
 107. Go, A.S., Mozaffarian, D., Roger, V.L., Benjamin, E.B., Berry, J.D., *Et al*. 2013. Heart disease and stroke statistics – 2013 update. *Circulation*. 127:e6-e245.
 108. Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., *et al*. 2007. Prevalence of Dementia in the United States: The aging, demographics, and memory study. *Neuroepidemiology*. 29:125-132.
 109. de Lau, L.M.L., Breteler, M.M.B. 2006. Epidemiology of Parkinson's disease. *The Lancet Neurology*. 5:525-535.