iNPH QUEST Study: **Qu**antifying a battery of Gait, Cognitive and Radiological **E**xaminations to improve identification of **S**hunt candidates from the cerebrospinal fluid **T**ap test

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Originality

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

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Statement of ethical conduct

In addition, ethical approval from the Hunter New England Human Research Ethics Committee, and co registration from the University of Newcastle Human Ethics Committee was granted for the clinical studies presented in this thesis. In each instance, participants were required to read an information statement and provide informed written consent prior to the collection of any data.

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5. **Gallagher R**, Bateman G Marquez J, Osmotherly P. Are gait changes linked to CSF flow changes in the Sagittal sinus? *Neuroradiology*. 2019, https//doi.org/10.1007/s00234-019-02192-2 published online ahead of print

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2. **Gallagher R**, Marquez J, Osmotherly P. Can gait and balance measures identify individuals who respond to a lumbar puncture tap test in patients with idiopathic normal pressure hydrocephalus (INPH)? *Fluids and Barriers of the CNS.* 2018;15 Suppl1(4):A47

3. **Gallagher R**, Bateman G, Marquez J, Osmotherly P. Is the sagittal sinus involved in idiopathic normal pressure hydrocephalus (INPH). Analysis of MRI CSF flow studies in patients undergoing a CSF tap test. *Fluids and Barriers of the CNS.* 2018;15 Suppl1(4):A48

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3. **Gallagher R**, Marquez JL, Osmotherly PG, 'Can gait and balance measures identify individuals who respond to a lumbar puncture tap test in patients with idiopathic normal pressure hydrocephalus?' Momentum 2017. Proceedings of Australian Physiotherapy Association Biennial Conference, Sydney (2017)

4. **Gallagher R**, Bateman G, Marquez J, Osmotherly PG, 'Is the sagittal sinus involved in iNPH? Analysis of MRI CSF flow studies in patients undergoing a CSF tap test(TT) for idiopathic normal pressure hydrocephalus (iNPH).' Hydrocephalus 2017 Kobe, Japan (2017)

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7. **Gallagher R**, Chiarelli PE, Marquez J, Osmotherly PG, 'iNPH QUEST Study: Quantifying a battery of gait, cognitive and radiological examinations to improve shunt response from the lumbar puncture tap test: Interim results', Proceedings of the Australian Physiotherapy Association Conference 2015, Gold Coast (2015)

8. **Gallagher R**, Osmotherly PG, Chiarelli PE, 'Idiopathic normal pressure hydrocephalus. Is there a role for physiotherapists in management?' Proceedings of the Australian Physiotherapy Association Conference 2013, Melbourne (2013)

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Glossary of abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
AMO	Admitting Medical Officer
AUC	Area under curve
BBS	Berg balance scale
CT	Computer tomography
CSF	Cerebrospinal fluid
ELD	External lumbar drainage
GRC	Global rating of change
ICP	Intracranial pressure
iNPH	Idiopathic normal pressure hydrocephalus
MRI	Magnetic resonance imaging
MDC	Minimal detectable change
MCID	Minimally clinically important difference
MoCA	Montreal cognitive assessment
PD	Parkinson's disease
SEM	Standard error of measurement
SSS	Superior Sagittal sinus
TE	Echo time
TR	Repetition time
TUG	Timed up and go

TUG-C	Timed up and go cognition
TT	Tap test
VP	Ventricular peritoneal
9HPT	9 hole peg test
10MWT	10 metre walk test

Thesis abstract

Idiopathic normal Pressure hydrocephalus (iNPH), a condition resulting in abnormalities of gait, cognition and continence, is treated by the placement of a ventricular peritoneal (VP) shunt to drain cerebrospinal fluid (CSF). To identify surgical candidates the CSF tap test (TT) was devised to mimic VP shunt insertion. The CSF TT involves drainage of a small volume of CSF to assess for symptom improvement. Additionally, measurements of CSF flow on MRI imaging have been devised to identify VP shunt candidates. Limited research has investigated assessing what outcome measures can identify change from a CSF TT. Neither the tests capable of definitively identifying change from a CSF TT nor the degree of change required on any test constituting a clinically important difference have been extensively investigated. Additionally, whether any measure on MRI CSF flow studies can identify change using outcome measures has not been explored.

This thesis aims to: 1. Identify a battery of standardised gait and balance outcome measures which can identify change from a CSF TT. 2. Identify a battery of standardised upper limb and cognitive outcome measures which can identify change from a CSF TT. 3. Develop minimally clinically important differences (MCIDs) for a battery of outcome measures. 4. Identify radiological markers on MRI CSF flow studies that are prognostic of response to CSF drainage. The ability of the Timed up and go (TUG), Timed up and go cognition (TUG-C), performance oriented mobility assessment (Tinetti), Berg balance scale (BBS), 10 metre walk test (10MWT), Montreal cognitive assessment (MoCA) and 9 hole peg test (9HPT) to identify change from a CSF TT was assessed.

These studies demonstrated that the TUG, TUG-C, Tinetti and BBS could identify change from a CSF TT. Calculated MCIDs were 3.63sec for the TUG, 2.60sec for the TUG-C, 4 points for the Tinetti and 4 points for the BBS represent MCIDs for improvement from a CSF TT. Additionally, we have shown that the measurements of the sagittal sinus circumference and area can differentiate improvement in gait as a result of CSF drainage. Further research is required to evaluate the utility of these MCID values in identifying improvement following VP shunt insertion.

Chapter 1 Introduction

1.1 Hydrocephalus and its subtypes

Hydrocephalus by definition means “water on the brain”.[1,2] Hydrocephalus represents the excessive accumulation of CSF within the brain resulting in neurological symptoms and can be defined as acute or chronic. [3] Acute hydrocephalus is often the result of trauma such as a penetrating injury or haemorrhage whereas chronic hydrocephalus may develop due to congenital abnormalities or delayed complications associated with trauma. Other causes include congenital abnormalities, or it may be idiopathic in nature.[4,5]

Hydrocephalus can be further defined as obstructive or communicating. Obstructive hydrocephalus is caused by a blockage within the ventricular system blocking the flow of CSF between ventricles and the subarachnoid space.[2] Communicating hydrocephalus occurs from a blockage of CSF flow from the sub arachnoid space into the venous and lymphatic systems. It is routinely considered to be a result of chronic changes within the central nervous system and presents with a gradual insidious development of symptoms. Obstructive hydrocephalus is typically associated with the sudden acute development of symptoms.[1]

Normal pressure hydrocephalus is so named due to the chronic communicating nature of its manifestation. Typically, with hydrocephalus, intracranial pressures are raised due to excessive CSF accumulation. However, in normal pressure hydrocephalus due the significant latency of time for symptoms to develop the brain parenchyma adapts to this excess CSF volume by compressing, allowing intracranial pressures to remain within a normal range.[6,7]

Normal pressure hydrocephalus can be divided into two forms, idiopathic and secondary.[8,9] The idiopathic form occurs for no identifiable reason whilst secondary normal pressure hydrocephalus occurs as a result of an identifiable cause such as congenital abnormality, trauma or haemorrhage.

Symptomatically, the two forms are similar and both present without rise in intracranial pressure as a result of the hydrocephalus.[6]

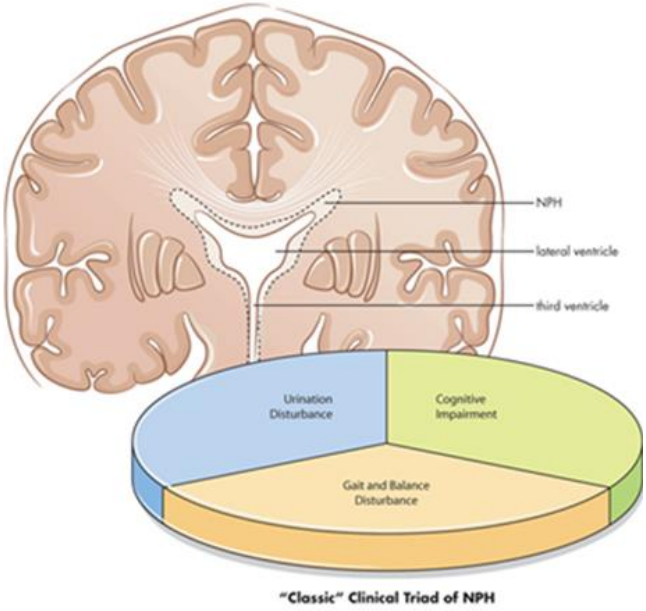
Idiopathic normal pressure hydrocephalus (iNPH) is a condition presenting in the geriatric population which results in a triad of symptoms of gait disturbance, incontinence and impaired cognition.[10,11] iNPH is classified as a chronic communicating hydrocephalus. It is typically diagnosed by the presence of these classic symptoms in addition to ventriculomegaly on radiological assessment, and normal CSF opening pressure on lumbar puncture. While the exact mechanisms remain unknown, it is believed the symptoms are produced by decreased absorption of CSF within the subarachnoid space resulting in increased CSF volume and, ventricular distension.[12]

Agreement on the prevalence of iNPH has not been established but has been calculated at between 15.2/100 000/ year to 21.9/100 000/year in North America. Prevalence estimates by age increase from 3.3 per 100,000 for people 50 to 59 years of age to 49.3 per 100,000 for people 60 to 69 years of age and 181.7 per 100,000 for people 70 to 79 years of age.[13] The incidence of iNPH has been estimated at 5.5/100 000 based on a Norwegian population [13] with a large increase in incidence with increasing age being identified. An incidence of between 3.74/100 000/year to 5.5/100 0000/year has also been determined in the United States.[13,14] iNPH is estimated to affect 9 to 14% of patients admitted into aged care facilities.[15] It has been further reported that iNPH could represent up to 5% of all dementia cases.[16] Current difficulty in diagnosis and assessment lies in differentiating the signs and symptoms of iNPH from other neurodegenerative disorders.[17] It is believed that iNPH is a major reversible cause of cognitive and mobility decline in the geriatric population.[18]

1.2 Symptoms of iNPH

Typically, iNPH will manifest with an insidious onset of rapid or progressive gait disturbance with associated cognitive impairment. Typically, the triad of symptoms presents in the later stage of disease progression. [19] Figure 1.1 demonstrates the classical triad of iNPH. Gait disturbance is typically the most common and pronounced symptom present for patients.[20] Patients presenting with gait disturbances as the major complaint have been shown to have a better prognosis for improvement in their symptoms.[19] Patients with minimal gait disturbance or significant cognitive impairment have been shown to have a poorer prognosis.[19] More recently, the triad of symptoms has been expanded to represent a phenotype seen in iNPH.[8] This includes impaired postural control, dynamic balance and impaired executive functioning.[6] The use of the term ataxia to describe gait can often be misleading with many iNPH sufferer's presenting with a shuffling gait pattern with reduced step length and foot clearance as opposed to a genuine ataxic pattern. This gait pattern is often likened to a Parkinsonian gait pattern.[15]

Figure 1.1 Classical clinical triad of iNPH [21]



The associated cognitive deficits have also evolved from original descriptions.[22] Initially likened to Alzheimer's disease (AD) in its cognitive profile, subtle differences in executive functioning and memory impairments have been identified differentiating iNPH cognitive deficits from AD.[22] These however only appear to be true for early stage cognitive deficits with end stage symptoms often mirroring symptoms of AD.[22]

Incontinence in iNPH is often described as an urge incontinence. [23] There has been some suggestion incontinence problems are a result of other symptoms of iNPH such as untimely gait, but evidence suggests urodynamic issues are also present in iNPH.[23] Detrusor overactivity has been shown to be a common cause of incontinence in frontal dementia and evidence of this cause in iNPH has also been demonstrated.[23] Lower urinary tract symptoms have been shown to be present in 93% of patients in one iNPH study with the presence of urinary urgency significantly higher than the presence of urinary incontinence, and overall reduced bladder activity noted before first sensation to void consistent with detrusor overactivity.[23]

The presence and progression of symptoms are often used as prognostic tools in determining the potential for successful outcomes following treatment. Gait impairments have consistently been shown to be the symptom most responsive to treatment.[24] Patients whose primary or only symptom is gait disturbance are often regarded as having the best prognosis from treatment.[25,26] Those with the development of the triad of symptoms or the presence of cognitive deficits as the primary symptom have the poorest response to treatment. [8,18]

1.3 Physiology of cerebrospinal fluid

The protective role of CSF in bathing the central nervous system has long been known.[2] The role CSF plays in the regulation of brain function, the development of dementia, and hydrocephalus continues to evolve. Normal CSF production accumulates at a rate of 0.4ml/min to a total volume of 140-160ml of CSF. [2] This volume is replaced approximately 3-4 times a day. Around 70% of CSF is produced in the choroid plexuses in the lateral ventricles with the remaining 30% produced in the 3rd and 4th ventricles.[2]

Typically, 25ml of CSF is located in the ventricles and 125-150ml of CSF is located in the sub arachnoid space.[1] The flow of CSF through the ventricular system and sub arachnoid spaces is thought to be dependent on arterial pulse waves through the cranial vault.[2] These pulse waves facilitate flow of CSF out of the sub arachnoid space and into the venous and lymphatic system via arachnoid villi granulations.

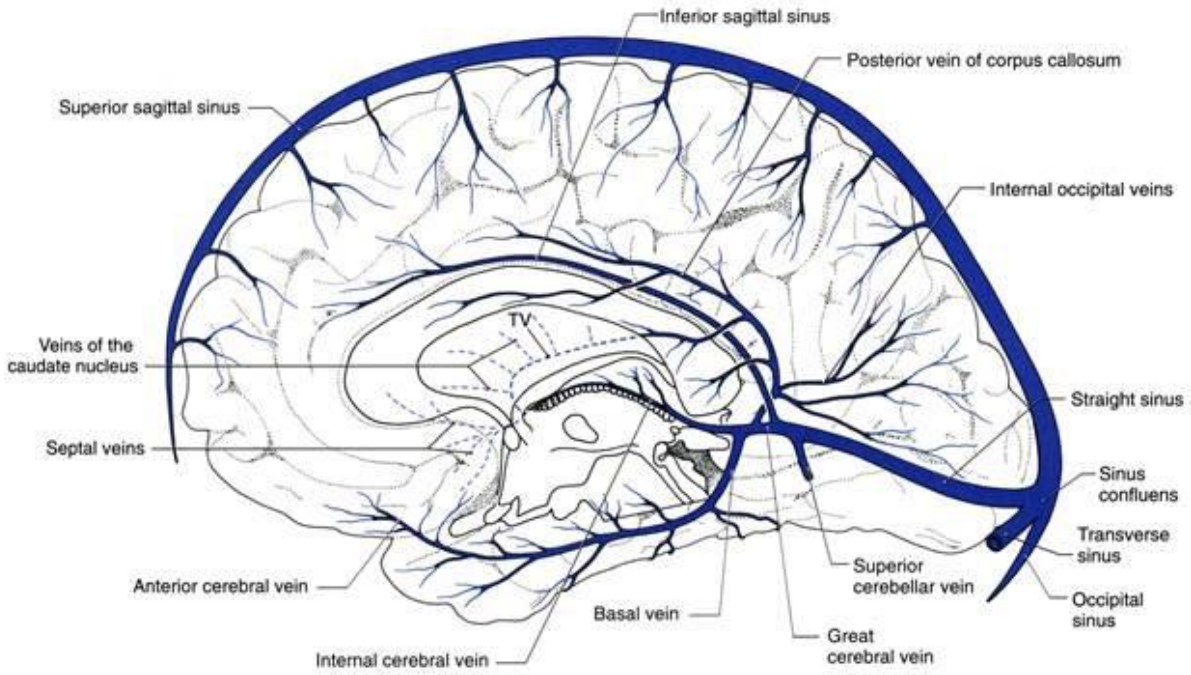
CSF absorption occurs through arachnoid granulations into the sinuses of the brain before being deposited into the internal jugular vein. The pressure differential between the sub arachnoid space and the internal jugular vein, which is around 3-5 mmHg plays a pivotal role in CSF absorption.[2] A small amount of CSF is absorbed through interstitial tissues, such as nerve meningeal sheaths and into extracellular fluid. This process of absorption is poorly understood but is known to exist due to symptoms present from other forms of hydrocephalus.[2]

1.4 Venous sinus system

The venous drainage of the cranial vault occurs through a series of veins know as sinuses.[1,2] The sinuses are triangular shaped vessels bordered by the dura mater and the endosteal bone of the cranium. The venous sinus system is made up of the superior sagittal sinus, the inferior sagittal sinus, the straight sagittal sinus, the sphenoparietal sinus, cavernous sinus, the occipital sinus, the transverse sinus and the sigmoid sinus.[27]

The sinuses collect CSF via arachnoid granulations and blood via the capillary network within the cranial vault and drain into the internal jugular vein. Figure 1.2 provides on overview of the sinus drainage within the cranium.

Figure 1.2 Sinus drainage of the cranium[28]



1.5 Aetiology of iNPH

Thickening and fibrosis of the arachnoid membrane resulting in decreased CSF absorption through arachnoid granulations has been postulated to be a primary cause of iNPH.[6] There is evidence to suggest that inflammation of arachnoid granulations is the mechanism which prevents CSF absorption.[6] Additionally, patients with iNPH have been shown to have significantly higher rates of co-existing vascular disease associated with their diagnosis of iNPH.[29,30] This suggests vascular changes and vascular disease are potentially associated with the development of iNPH.

Other findings consistently seen in iNPH include:

- Ventricular ependymal disruption
- Subependymal gliosis
- Multiple white matter infarcts
- Pathological changes consistent with Alzheimer's disease

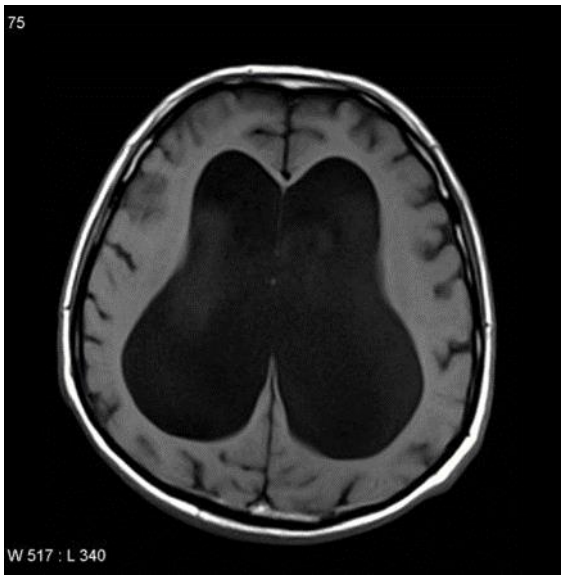
These changes may or may not be present depending on the stage of iNPH. Several studies have identified pathological findings of iNPH.[6] Table 1.1 provides a summary of findings by paper.

Table 1.1 Summary of pathophysiological findings in iNPH by publication [31]

Author(year)	Meningeal thickening	Inflammation of arachnoid villi	Subependymal gliosis	Alzheimer's pathology	Vascular pathology
Deland et al (1972)	Present	Present	Present	Absent	Absent
Stein and Langfitt (1974)	Absent	Absent	Absent	Present	Present
Earnest et al (1974)	Not assessed	Not assessed	Absent	Absent	Present
Di Rocco et al (1977)	Present	Absent	Present	Present	Present
Bech et al (1999)	Present	Absent	Absent	Present	Present
Golomb et al (2000)	Absent	Absent	Absent	Present	Absent
Bech-Azeddine et al (2007)	Absent	Absent	Absent	Present	Present
Hamilton et al (2010)	Absent	Absent	Absent	Present	Present

While the above table summarises the changes present in iNPH, the exact reason for the manifestation of these symptoms is yet to be established. To date, no consensus has been reached on the definitive aetiology of iNPH. It is entirely plausible that iNPH may result from a multifactorial etiological process. However a single causative factor has not been ruled out.[6]

Figure 1.3 Ventromegaly on MRI scan consistent with iNPH [32]



1.6 Pathophysiology in iNPH

In iNPH, CSF turnover reduces to around 1.5 times a day.[1] This results in a rise of overall CSF volumes to around 200mls. Figure 1.3 provides a representation on MRI of ventromegaly caused by excessive CSF volumes within the lateral ventricles. iNPH is classified as a communicating hydrocephalus due to the absence of obstruction to impede the flow of CSF around the brain.[2,33] It is postulated that decreased CSF absorption thorough arachnoid granulations is the primary cause of increased CSF volumes in iNPH. Measurements of resistance to CSF outflow are consistently shown to be elevated in iNPH.[34] The exact mechanism for this however remains undetermined. Links to vascular disease and neurofibrary bundle accumulation have been hypothesised as possible causes. [35,36] A long term atherosclerosis risk study also demonstrated elevated systolic blood pressure and pulse pressure are associated with increased ventricular size.[34,37]

1.7 Cardiovascular risk factors

Multiple cardiovascular risk factors have been established for the development of iNPH. Vascular abnormality has been identified as a potential risk factor leading to the manifestation of iNPH.[38,39] Age is a clear risk factor for iNPH with the majority of sufferers being over the age of 75. Other proposed risk factors include the presence of neurofibrary bundles within the CSF, diabetes mellitus, and low serum levels of high density cholesterol.[19] All of these risk factors are risk factors of vascular disease which suggests that vascular pathology may play a significant role in the manifestation of iNPH.[40] It has been established that vascular risk factors of hypertension, hyperlipidaemia, diabetes, abdominal obesity and physical inactivity are all over represented in iNPH patients compared to matched controls.[29] Furthermore, it has been shown that peripheral vascular disease and cardiovascular disease are also over represented in iNPH patients. Regression modelling adjusted for age and sex have shown that hyperlipidaemia, diabetes and abdominal obesity are independently associated with iNPH.[29]

Overall, it has been demonstrated that up to 24% of iNPH diagnoses may be explained by the presence of vascular risk factors based on population attributable risk calculations.[30] Conflicting evidence exists in relation to the impact of cardiovascular risk factors on treatment outcome, with one study showing 59% of patients with cardiovascular disease improved after shunting compared to 79% of shunt patients with no cardiovascular risk factors. However, further research showed that cardiovascular risk factors has no impact on surgical outcome at 3 years despite patients with risk factors having higher modified Rankin Scores pre operatively.[30] Similarly, patients with cardiovascular risk factors have been shown to have post-operative improvements akin to patients without cardiovascular disease despite patients with cardiovascular risk factors tending to have lower scores pre and post operatively on all testing regimes.[41] Survival analysis in this population showed no statistical differences were present between patients with no, mild and severe cardiovascular risk factors despite a trend towards better survival rates for no cardiovascular risk factors.[41]

1.8 Comorbidities in iNPH

The regular presence of comorbidities can make diagnosis of iNPH challenging. Common comorbidities are often incorrectly diagnosed as the primary cause of a patient's complaint prior to a iNPH diagnosis.[42,43] This can delay definitive management of iNPH. Common comorbidities include Parkinson's disease, Alzheimer's disease, frontal dementia, Lewy body dementia and other forms of mild cognitive deficits, psychiatric disease, vascular disease, diabetes mellitus and musculoskeletal disease.[8,33] It has been reported that up to 40% of patients diagnosed with iNPH have AD coexisting based on histological lesions.[42] Higher degrees of cognitive and gait dysfunction are associated with a higher likelihood of coexisting AD.[42] The presence of comorbidities often has a significant impact on prognosis and response to iNPH management.

Musculoskeletal diseases such as osteoarthritis have been demonstrated to be a significant comorbidity in iNPH. The presence of osteoarthritis and other musculoskeletal diseases potentially may mask the presence of iNPH symptoms with the presence of gait difficulties often believed to be associated with co-existing disease.[43]

1.9 Diagnostic criteria of iNPH

Two distinct guidelines have been developed to assist with the diagnosis of iNPH. International guidelines were developed in 2005 through the collaboration of delegates from America, Europe and Japan.[44] In 2012 Japanese researchers released their own updated guidelines.[6] These guidelines are summarised in Table 1.2. Currently the international guidelines form the basis for current evidence in the majority of studies arising from outside of Japan.[45]

An abridged version is utilised in future chapters of this thesis.

Table 1.2 Summary of iNPH guidelines

2005 International Guidelines[44]	2012 Japanese Guidelines[6]
Probable iNPH • Onset > 40 years of age • Duration of at least 3-6 months • No evidence of any cranial trauma or pathology or secondary NPH • No other diagnosis to explain the symptoms and their progression • Radiological imaging showing: - Evans index > 0.3 - Enlargement of temporal horns of lateral ventricles - Altered brain water content on CT or MRI not attributable to other diagnosis's • Gait ataxia with specific signs • Cognitive changes with specific signs • Incontinence with specific signs	Probable iNPH • Meets all requirements for possible iNPH • CSF pressures of 200mmH_2O or less • Imaging showing narrowing of sulci and subarachnoid spaces over midline surface with gait disturbance present Improvement of symptoms after CSF drainage
Possible iNPH • Subacute mode of onset • Begin at any age • Non progressive in nature • Radiological signs that may be due to atrophy • Gait ataxia, incontinence or dementia alone • CSF opening pressure outside expected range	Possible iNPH • Onset > 60 years • Evans index > 0.3 • Symptoms not explained by other diagnosis • No medical history able to explain ventricular dilation Supportive features of possible iNPH • Gait ataxia most prominent feature followed by cognitive impairment and urinary incontinence • Sylvain fissures and basal cistern enlarged on imaging • Co-existence of Parkinson's or Alzheimer's disease in mild forms

Unfortunately, diagnosis does not ensure response to treatment. iNPH can be further divided into shunt responsive iNPH and non-responsive iNPH.[6,44] This often confounds diagnosis and management. The primary treatment option is the insertion of a ventricular peritoneal (VP) shunt and appropriateness of this intervention can only be determined through specific tests to temporarily mimic the effects of a shunt.[8,12]

1.10 Assessment of iNPH

Assessment routinely occurs via radiological means such as CT and MRI imaging, combined with a physical examination. A standard neurological examination identifies underlying physical signs of iNPH, but does not identify patients who may or may not respond to surgical intervention.[17,38]

Radiological examination by CT and MRI scans are required to confirm a diagnosis of iNPH. The presence of an Evans index greater than 0.3, indicative of ventriculomegaly, is required for a iNPH diagnosis.[6,8] An Evans index is the ratio of maximum width of the frontal horns of the lateral ventricles and maximal internal diameter of skull at the same level employed in axial CT and MRI images.[8] In addition to plain CT and MRI, MRI CSF flow studies are often employed to identify limitations in CSF flow. Research exists suggesting CSF flow through the cerebral aqueduct is affected in iNPH and may be predictive of identifying positive response to surgical treatment.[46,47]

Supplementary tests intended to identify surgical responders compared to non-responders have been developed. The purpose of these tests is to temporarily mimic the potential effects of surgical intervention by draining CSF.[26,48] Two main forms currently used are external lumbar drainage (ELD) and the CSF tap test (CSF TT).[26] ELD is performed by a lumbar drain and aims to remove high CSF volumes in excess of 500mls over 3-5 days. Patients are admitted and remain on bed rest during drainage. When the lumbar drain is clamped symptomatic assessment identifies if improvement has occurred.[11,18,26] The CSF TT, often performed by a one-off lumbar puncture, aims to drain a smaller

amount of CSF (30-50ml). The CSF TT is often preferred over ELD due to shorter timeframes, the ability to be performed as an outpatient, and reduced likelihood of complications due to bed rest.[49,50] Differences in specificity and sensitivity however have resulted in lower negative prediction values from the CSF TT compared to ELD. [9,50] Use of the two methods varies across regions and countries based on local clinical preference.

1.11 Treatment

The primary treatment option for NPH is the insertion of a VP shunt by a neurosurgeon. [7,12,19] The aim of the VP shunt is to provide ongoing drainage of excessive CSF to reverse symptoms. [5] This procedure involves the insertion of a small catheter into the right lateral ventricle and passing it subcutaneously behind the patient's right ear to a valve. Alternatively, in some parts of the world, the use of a lumbar peritoneal shunt is used in place of the VP shunt. Efficacy in outcomes between VP and lumbar peritoneal shunts are reportedly similar.[51,52] A VP shunt involves a valve that is programmed to measure intracranial pressures (ICP) and allow the flow of CSF when the set pressure has been exceeded. A second catheter runs from the valve subcutaneously to the peritoneal cavity into which the CSF drains.[13]

A diagnosis of iNPH does not guarantee patients will respond to VP shunt treatment. Determination of who will respond to shunt surgery is made through clinical evaluation of radiological findings along with results from supplemental testing such as the CSF TT or ELD. Patients deemed to be responders to the CSF TT with radiological evidence supporting a diagnosis of iNPH often proceed to VP shunt insertion.

Complications with surgery are common and occur in approximately one third of patients.[7,53] These are often a consequence of the technical difficulty of managing the valve pressure. Shunts typically have pressure valves which open when ICP rises above normal, thus allowing CSF draining to normalise

ICP. As ICP's remain normal in iNPH valve settings must be adjusted compared to other forms of hydrocephalus where ICP's are raised. Should the valve pressure be set too high no drainage will occur and no benefits gained.[19,54] Similarly setting a pressure too low will result in over drainage and complications ranging from headaches to subdural haematomas.[3]

Shunt revision is one of the most common neurosurgical operations, with common failure of shunts at around 5 years after insertion.[13,54,55] Shunt malfunction has been shown to occur in 15% of shunts.[5] One of the largest predictors of shunt failure is advanced age.[5] In an elderly population the rate of shunt malfunction is often exacerbated by comorbidities. The primary problems include adhesions which obstruct CSF flow through the shunt and the choroid plexus growing into the catheter.[3]

1.12 Treatment limitations

Despite the growing volume of evidence assisting the diagnosis of iNPH and guiding management, the odds of successful treatment of the condition have remained unchanged for some time.[56] Determination of patients who would benefit from surgery remains subjective despite the development of an array of supplementary tests.

Reports of improvement post-surgery remain constant across a number of studies.[54,57,58] A general rule of one-third of patients improving after surgery, one-third plateauing and another third continuing to deteriorate after surgery is regularly reported.[24,39,54] This is due to the limited ability to differentiate iNPH from other non-treatable causes of hydrocephalus and complications rates associated with VP shunts.

1.13 Tap tests limitations

Supplemental tests such as the CSF TT have been developed to increase the accuracy of identifying patients who would benefit from surgery with the rationale being a positive response to supplemental testing will likely result in a positive response to surgery. [26,59,60] This however has proven problematic with reported low negative predictive values of CSF TT in excluding shunt surgery in isolation.[6,26]

An additional limitation of supplemental tests has been the subjective determination of whether the response is positive and warrants surgical intervention.[11] No clear criteria have been reported on what testing should be completed to assess symptom changes following the CSF TT. To date no work has been undertaken to determine the predictive validity of the CST TT in any form. Furthermore, no minimal response has been identified on testing completed as a part of the CSF TT to determine response status.[18]

Chapter 2 Thesis research design

2.1 Study rationale

Limitations related to determining when a patient with iNPH has genuinely responded to a CSF TT has facilitated the need for this program of research. Guidelines are clear in relation to diagnostic criteria and the suitability of the use of supplemental testing such as the CSF TT but no consistent evidence exists to define what constitutes a positive or negative CSF TT and therefore the recommendation for VP shunt insertion remains subjectively based on the preferred practices of the admitting medical officers. This results in inconsistencies for patients seeking treatment.

This thesis aims to provide evidence for clinicians managing patients with iNPH to guide the implementation of assessments which can identify change resulting from a CSF TT and the extent of improvement required to determine that a positive response has occurred.

To date, no research has been conducted to identify outcome measures which can identify change resulting from a CSF TT, nor to determine meaningful scores such as minimally clinically important differences for these measures. The ability of MRI CSF flow studies to identify improvement of symptoms has not been explored in relation to the CSF TT.

This series of studies will provide evidence to support decision making in relation to outcome measures which should be used to assess improvement from a CSF TT, with a clear delineation of what constitutes a positive or negative response, and what this will mean should the patient undergo VP shunt insertion.

2.2 Research question

Can a battery of outcomes measures assessing gait, balance, cognitive, upper limb and radiological changes identify improvements from a CSF TT for iNPH? What constitutes a meaningful improvement by which to determine improvement?

2.3 Research aims

This research project aims to achieve the following:

1. Identify a battery of standardised gait and balance outcome measures which can identify change from a CSF TT

2. Identify a battery of standardised upper limb and cognitive outcome measures which can identify change from a CSF TT

3. Develop minimally clinically important differences for the above battery of outcome measures

4. Identify radiological markers on MRI CSF flow studies that are prognostic of response to CSF drainage

2.4 Participant inclusion/ exclusion criteria

Inclusion criteria for the study is as follows:

1. People admitted to the participating site for a CSF TT for the consideration of a ventricular peritoneal shunt for management of iNPH
2. A diagnosis of iNPH consistent with 2005 international iNPH Guidelines[44]

Exclusion criteria are:

1. Inability to walk 10m with a mobility device
2. Inability to undergo a MRI*
3. Inability to provide informed consent or no next of kin available to provide consent

*Where patients were unable to undergo a MRI they may still have been enrolled in the study to complete arm 1 and arm 2 (see below).

2.5 Ethical considerations

This study was approved by the HNE Human Research Ethics committee. Reference number: **13/06/19/4.02.**

This study was co registered by The University of Newcastle Ethics committee Reference number: **H-2013-0384.**

2.6 Study design

This is a prospective observational study with three distinct arms to its design as outlined below.

Arm 1 – Gait and balance outcome measures

Patients underwent the following four balance and gait assessments before and after a CSF TT:

1. Berg Balance Scale (BBS)

2. Performance Oriented Mobility Assessment (Tinetti)

3. 10m walk test (10MWT)

4. Timed Up and Go (TUG)

Arm 2 – Cognitive and upper limb outcome measures

Patients underwent the following cognitive and upper limb examinations before and after a CSF TT:

1. Timed Up and Go cognitive (TUG-C)

2. 9 Hole Peg Test(9HPT)

3. Montreal cognitive assessment (MoCA)

Tests 1 and 2 were completed by a physiotherapist. An occupational therapist completed test 3.

Arm 3 - Radiological investigation

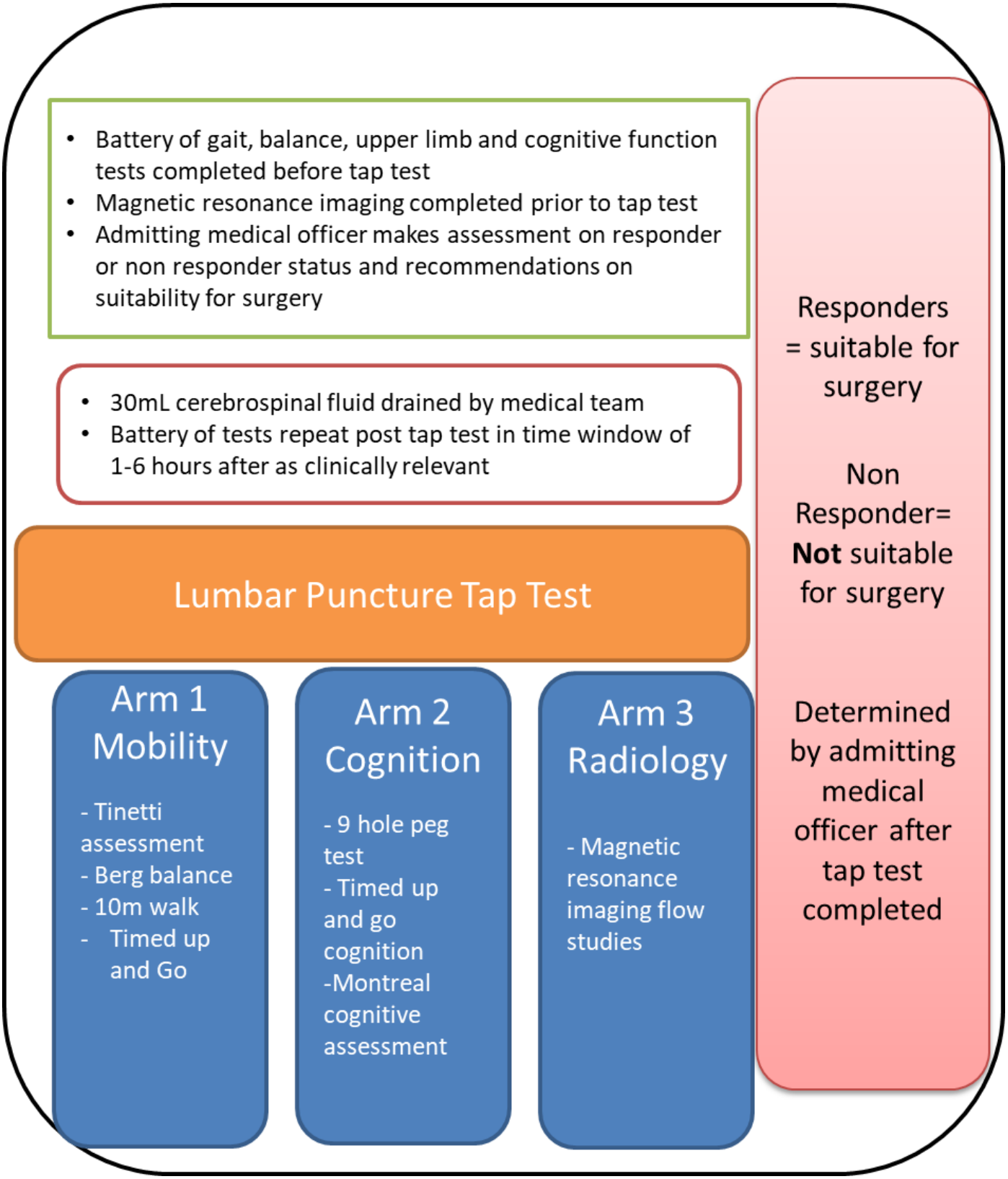
In addition to a CSF TT, patients underwent an MRI with CSF flow studies included in the sequencing of the MRI. The following variables were collected: aqueduct stroke volume, aqueduct net flow, arterial stroke volume, compliance ratio, arterial inflow, straight sinus flow, sagittal sinus flow, superior sagittal sinus flow, sagittal sinus stroke volume, sagittal sinus to stroke volume ratio, sagittal sinus area, sagittal sinus circumference and circularity.

All of the above collected information was made available to the patient's admitting medical officer.

2.7 Recruitment numbers

Power calculations indicated a total of 74 patients undergoing a CSF TT were required to achieve statistical significance, with an alpha value of 0.5 and power of 80%, to answer research aims 1 to 3 as listed above. These calculations were based on previously reported minimal detectable change scores from the TUG reported in previous studies. The TUG represented the highest number of recruitments for the outcome measures utilised.[61] In the absence of any MDC calculations in an iNPH population it was determined to utilise an MDC from a Parkinson's population due to similarities present between the gait patterns of these two conditions. The TUG result was selected for powering purposes as this required the maximum sample size of all calculations allowing a sample size which would ensure adequate powering was present for all tests

Figure 2.1 Study design and arms



Chapter 3 Idiopathic normal pressure hydrocephalus: what is the physiotherapist's role in management?

The body of this chapter has been published in *Physical Therapy Reviews*. [62]

3.1 Synopsis

The evidence supporting specific testing of gait and mobility in regard to CSF TT is limited and disseminated across a variety of scientific journals. Given that physiotherapists are routinely involved in assessing changes in gait and balance related to the CSF TT, a synthesised single source for the available evidence was required to allow for easy interpretation of the evidence which is currently available in relation to the suitability of specific outcome measures. The aim of this review was to synthesise the evidence that was available at the time of publication in relation to the physiotherapist's involvement in the CSF TT.

This summary examines the overall physiotherapy management of patients with iNPH who are considered for the insertion of a VP shunt. Due to the paucity of evidence specifically related to the CSF TT, comment is provided in relation to other forms of CSF drainage to assess iNPH.

This synthesis of evidence allows discussion of the future implications for research into the area of physiotherapy and iNPH which are ultimately addressed in following chapters of this thesis. Additionally, based on this narrative reviews findings outcome measures which have potential to be utilised in relation to the CSF TT are listed in table 3.3

3.2 Abstract

Background, Idiopathic normal pressure hydrocephalus (iNPH) is a condition resulting in a symptom triad of gait ataxia, cognitive impairment and urinary incontinence. iNPH presents a diagnostic and management dilemma such that management involves the placement of a ventricular peritoneal (VP) shunt to which not all patients will respond. Cerebrospinal fluid (CSF) drainage tests such as the lumbar puncture tap test (TT) provide a prognostic indication of response to shunting. However, determination of what constitutes a positive response to shunting is not clearly defined. While gait improvement following TT has been identified as a possible prognostic indicator, the efficacy of such measures in this clinical population has not been tested. **Objectives:** To explore the literature related to gait and balance changes associated with iNPH and to identify the possible role physiotherapists might play in the diagnosis of patients with iNPH. **Major findings:** Gait changes in iNPH patients have been well documented and improvement following TT has been identified as a strong prognostic indicator of improvement following VP shunt insertion. No research has been identified looking directly at balance changes in patients with iNPH following TT or VP shunt insertion and the efficacy of objective gait assessments in this patient population have not been evaluated. No studies have determined the predictability of improvement after shunting based on measured gait improvements following TT. **Conclusions:** Physiotherapists are expertly placed to be involved in the assessment of symptoms of iNPH. However, further research is required to validate balance and gait assessment in this patient group to determine if prediction of shunt outcome is possible using gait assessment after the TT.

3.3 Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition with a triad of symptoms including gait ataxia, incontinence and impaired cognition. [11,19] iNPH is typically diagnosed in the presence of this classical triad of symptoms together with ventriculomegaly on imaging, and elevated within normal cerebrospinal fluid (CSF) opening pressure on lumbar puncture.[10] iNPH was first described in 1965 by Hakim and Adams in a series of case presentations where symptoms improved following removal of CSF.[63] Debate about management and diagnosis of iNPH continues and it is postulated to be a major reversible cause of cognitive and mobility decline in the geriatric population.[18] Cognitive changes in iNPH are suggestive of subcortical dementia due to its presenting symptoms and iNPH is considered a treatable form of dementia.[19 8] Often iNPH manifests in the presence of a diagnosis of Alzheimer's disease or other form of dementia and links have been drawn between the pathophysiology of the two.[36,64]

Two forms of normal pressure hydrocephalus have been described: idiopathic and secondary. iNPH occurs in the geriatric population in the absence of any pre-existing factors or insults to explain the change in CSF dynamics. Secondary normal pressure hydrocephalus occurs as a result of previous neurological insult such as trauma, stroke, or congenital abnormality and may occur at a younger age.[19] This delineation of diagnosis has only recently been articulated in research, contributing to the lack of consensus on management of iNPH. [26] Agreement on the prevalence of iNPH has yet to be established, but has been calculated at between 15.2/100 000/year to 21.9/100 000/year. An incidence of between 3.74/100 000/year to 5.5/100 0000/year has also been calculated. [13,14] iNPH is estimated to affect between 9% and 14% of patients admitted into care facilities. [15]

Current management options focus on the removal of excessive CSF via insertion of a ventriculo-peritoneal (VP) shunt. Diagnostic criteria for iNPH and criteria for predicted responsiveness to shunt placement are not always consistent. [6,19,65] Consensus is lacking in relation to a set of definitive diagnostic criteria, although attempts have been made to develop these.[8] Diagnosis is achieved

through a combination of clinical and radiological signs.[8] A further dilemma for clinicians is that a diagnosis does not always result in a positive response to treatment.[8] To overcome this, supplementary tests involving the drainage of CSF have been developed to identify potential responsiveness to shunting.[44] However, determination of who might benefit from removal of CSF via the insertion of a VP shunt remains dubious.[7,54] Several supplementary tests have been used, including drainage techniques such as the CSF tap test (TT) and external lumbar drainage (ELD), as well as radiological investigation including MRI flow studies and radionuclide cisternography.[6,19,38] The CSF TT, the most commonly used procedure, aims to identify patients most likely to respond to shunt insertion by removal of approximately 30-80mls of CSF, and assessing symptom change.[6,38,50]

Controversy remains regarding which measured parameters might determine a patients possible response to the CSF TT.[44] Physiotherapists are regularly called upon to assess gait and balance before and after patients undergo CSF TT to determine improvement.[11] However little evidence exists around the accuracy of such assessments and no validation of standard physiotherapy instruments such as the Timed up and go, 10 metre walk test or Berg balance assessment has been validated in this patient group. [50]

3.4 Diagnosis and management of iNPH

Since its description in 1965, consensus on accurate diagnostic criteria for iNPH has been lacking. Previously, emphasis was placed on shunt responsiveness as a diagnostic criterion, with true iNPH said to be that which responded to shunt placement.[6,8,19,39] However current guidelines do not make reference to shunt responsiveness in diagnostic criteria. Rather it is suggested that iNPH should be considered as a diagnosis in any patient with an insidious onset of the symptom triad.[6,8,44] Typically, patients who have had symptoms less than 18 to 24 months have the greatest potential to respond to shunt placement.[54]

Accurate diagnosis of iNPH requires the coexistence of signs from a patient's clinical history, together with physical and radiological examination. The presence of ventromegaly on CT or MRI scan with an Evan's index > 0.3 is considered a key factor in diagnosis, but not in isolation. Evans index is a measure of the ratio of maximum width of the frontal horns of the lateral ventricles to the maximum width of the inner table of the cranium.[6] Patients are required to have a CSF opening pressure in the range of 5-18mm Hg on lumbar puncture.[6,8] While the current guidelines, given in Table 3.1, differ regarding such factors as the minimum age and duration of symptoms, correlation exists between all other criteria. Common criteria are listed below.

A: Onset

- Insidious
- Origin after 40 yrs. of age
- Minimum duration 3-6 months
- No evidence of an incident event such as head trauma, intracranial haemorrhage, meningitis or similar conditions
- No medical or psychiatric condition sufficient to explain the presenting symptoms

B: Clinical signs considered mandatory for diagnosis:

- Gait abnormality
- Decreased motor speed

C: Cognition changes considered mandatory for diagnosis:

- Decreased attention or recall
- Impaired executive functioning or multi step functionin

D: Urological signs present unable to be explained by other underlying condition of which two must be present:

- Increased urinary urgency characterized by pressing need to void
- Increased urinary frequency (>6 voids in a 12 hour period)
- Nocturia (> 2 voids overnight)

Table 3.1 Diagnostic criteria based on published guidelines (abridged)

Marmarou 2005[19]	Mori and Ishikawa 2012[6]
Probable iNPH • Onset > 40 years of age • Duration of at least 3-6 months • No evidence of any cranial trauma or pathology or secondary NPH • No other diagnosis to explain the symptoms and their progression • Radiological imaging showing: - Evans index > 0.3 - Enlargement of temporal horns of later ventricles - Altered brain water content on CT or MRI not attributable to other diagnosis's • Gait ataxia with specific signs • Cognitive changes with specific signs • Incontinence with specific signs	Probable iNPH • Meets all requirements for possible iNPH • CSF pressures of 200mmH_2O or less • Imaging showing narrowing of sulci and subarachnoid spaces over midline surface with gait disturbance present Improvement of symptoms after CSF drainage
Possible iNPH • Subacute mode of onset • Begin at any age • Non progressive in nature • Radiological signs that may be due to atrophy • Gait ataxia, incontinence or dementia alone • CSF opening pressure outside expected range	Possible iNPH • Onset > 60 years • Evans index > 0.3 • Symptoms not explained by other diagnosis • No medical history able to explain ventricular dilation Supportive features of possible iNPH • Gait ataxia most prominent feature followed by cognitive impairment and urinary incontinence • Sylvain fissures and basal cistern enlarged on imaging • Co-existence of Parkinson's or Alzheimer's disease in mild forms

3.5 Pathophysiology of iNPH

Currently there is no viable model related to the development and pathophysiology of iNPH.[6] The manifestation of iNPH has been postulated to be caused by CSF circulatory failure and impaired clearance of CSF through arachnoid granulations.[36] Tenuous links have also been postulated between the pathophysiology of iNPH and Alzheimer's disease, based on the connection between altered CSF dynamics and the presence of amyloid beta in interstitial brain fluid.[64] Currently, neither of these theories have compelling evidential support.

Links have been demonstrated between vascular pathology and iNPH.[66] Association between iNPH and; arterial hypertension along with diabetes mellitus have been demonstrated. It has been postulated that arterial hypertension may result in increased white matter lesions contributing to the pathogenesis of iNPH. This hypothesis however, remains unproven.[66] It is possible that common links exist between the pathogenesis of Alzheimer's disease, iNPH and vascular disease. However cause and effect of any common pathogenesis remains unproven.[66]

Normal CSF production has been calculated at a rate of 0.4ml/min, the average human adult has a CSF volume of around 150-160ml with a turnover of roughly 4 times the volume/day. CSF volume and turnover have been shown to be impaired in iNPH populations, with CSF volumes rising to around 200mls and turnover decreasing to less than 1.5 times the volume per day. This decrease in clearance has been postulated to be a result of increased resistance to the clearance of CSF.[64]

The pathogenesis of the triad of symptoms seen in iNPH has not been well established. It was initially theorised that ventricular enlargement caused compression of pyramidal upper motor neuron fibres in the corona radiate.[10] This however has been questioned by electromyographic evidence showing sub cortical involvement by a disturbance in the phased activation of muscles and abnormally increased activity in antigravity muscles.[8,39] Rather, gait ataxia is seen as suggestive of a subcortical motor control issue rather than a pyramidal tract disturbance.[8] Similarly the frontostriatal pathways have been implicated in the development of dementia in iNPH.[63]

3.6 Determining suitability for shunting of iNPH

Supplemental tests are used to determine the suitability of patients for shunting in the management iNPH. Testing takes two forms: drainage methods and evaluation by imaging. Identification of patients who improve with CSF drainage may be prognostic in determining a positive outcome following shunt insertion.[24] Commonly used CSF drainage techniques include the CSF TT and ELD.[(11)] MRI flow studies have been developed and tested with conflicting results.[7] Links have been postulated between aqueductal CSF flow rates and iNPH, with changes in flow being identified following shunting.[67] MRI flow studies looking at overall CSF stroke flow may be of benefit, however prognostic links are yet to be made between aqueductal CSF flow or CSF stroke volume and shunt responsiveness.[7,67]

The CSF TT is the most commonly used diagnostic measure due to its simplicity, short time frame and easy repeatability. The CSF TT has been shown to be highly prognostic of response to shunting with positive predictive values between 94% and 100% reported, but poor sensitivity between 26% and 61% makes the CSF TT unreliable to exclude response to shunt. One study reported up to 58% of responders to shunting potentially being missed if a CSF TT had been used alone.[6,26] In comparison, ELD has been shown to have sensitivity ranging from 57% to 100% with a positive predictive value of 75 to 92%.[6,26] Improvement in gait following CSF TT drainage has been demonstrated to occur as early as 30 minutes and up to 24 hours after the intervention.[64] To date, the CSF TT has not undergone any prospective clinical evaluation to determine what might be considered significant improvement in a patient's symptoms.[15,36] While it is agreed that there is need for measured improvement in gait or cognition following CSF TT, no criteria has been suggested to establish the minimum magnitude of clinically significant improvement.[(11)] The importance of measured clinical improvement in symptoms underpins the assumption that improvements measured after the CSF TT are likely to be replicated following shunt insertion.[19,38]

ELD consists of draining 10mls/ hr of CSF continuously over a period of 72 hours. It was theorised that the increased amount of CSF drainage would result in increased sensitivity and specificity.[10,44]

Sensitivity and positive predictive value have been shown to be higher with ELD compared to the CSF TT.[44,54] However, a lack of validated criteria to determine a positive test outcome also limits ELD. There is increased risk of complications for patients undergoing ELD due to the prolonged period of bed rest required. These include the risk of spinal catheter dislodgement leading to over drainage of CSF.[26] The presence of cognitive impairment might also impair patients' ability to remain flat and idle for 72 hours, impacting on the results of ELD. Another factor that contributes to be ELD being used less frequently clinically than CSF TT is the need for hospital admission which adds significantly to the cost of ELD.[6] It is worth noting that to date, no evaluation of either CSF drainage technique has occurred to healthy aged match controls.

3.7 Gait changes in iNPH

Gait changes associated with iNPH have been described as a motor apraxia of gait in the absence of sensory or motor weakness.[18] Analysis of gait patterns before and after shunting have identified changes in velocity, dual stance time, stride length, stance width and cadence.[15,18] A summary of these changes is provided in Table 3.2. Similarities have been noted between the gait abnormalities identified with iNPH and those described in Parkinson's disease, namely freezing and shuffling gait.[11,12,39,55,68]

Guidelines developed in 2005 suggest for a diagnosis of iNPH a minimum of two of the following gait features must be present and not attributable to other conditions: decreased step length, decreased step height, decreased cadence, increased trunk sway, widened base of support, out toeing with walking and e*n bloc* turning (turning requiring three or more steps to turn 180 degrees). These abnormal gait signs presenting in patients with iNPH form the basis of physiotherapists' assessment of patients who may benefit from shunting.[15]

Table 3.2 Gait symptoms currently ascribed to iNPH in the literature

Study	Symptoms described
Ravdin 2008[25]	Narrow Base of Support
	Shortened step length
	Slow turning
	Tendency for falling
	Decreased cadence
Stolze 2001[68]	Decreased gait velocity
	Decreased stride length
	Widened Base of Support
	Externally rotated feet
	Decreased step height
Warnecke 2009[15]	Decreased Velocity
	Decreased Cadence
	Decreased stride length
Williams 2008[18]	Increased dual stance time
	Decreased cadence decreased velocity
	Decreased mean velocity

3.8 Validation of upper limb coordination measures, gait and balance currently used in patients with iNPH

Standardised tests that are administered by physiotherapists have been postulated to identify improvements in patients' gait and mobility following CSF drainage.[11] Tests which have been suggested to date include the performance orientated mobility assessment (Tinetti), timed up and go (TUG), 10 metre walk test, and the 9 hole peg test.[11] The Tinetti assessment consists of two components: balance and gait. Scores are combined from the two sections to provide an overall score.[69] The TUG is a measure of the time required for a patient to rise from an armchair, walk to a marker placed 3 metres away and return to sitting in the chair. The 9-hole peg test is performed bilaterally and measures the time taken for a patient to place 9 pegs into a board and remove them again.[70]

The efficacy of upper limb responsiveness to the CSF TT has been investigated. While the 9 hole peg test has been identified as one potential option, investigations by Feik showed no improvement after three days of ELD, reporting the lack of change may either reflect a lack of change in psychomotor speed over a period of time or poor sensitivity.[11] In an uncontrolled study, potential identifiable improvement with drawing and tracing tasks was described in 42 patients by Tsakanikas.[71] Responders to CSF TT were reported to have significant improvements in upper limb speed and coordination evidenced by a 12% decrease in the time required to trace a prescribed line pattern. Reported sensitivity was 76%, but specificity remained low at 44%.[71] No objective scale was used to quantify perceived improvements or to compare responders. No differences have been identified using other upper limb tests. While results of upper limb testing have been claimed to support their inclusion as part of the CSF TT assessment, the lack of efficacy demonstrated in the tracing tasks performed may in fact be due to the floor effect of tests, since many patients are likely to be unable to successfully complete such tests at baseline.[71]

Validation of the Tinetti and TUG to identify change after three days of ELD has been undertaken. Feik demonstrated statistically significant change with the Tinetti and TUG in 87 patients.[11] Patients were subject to two days of CSF pressure monitoring followed by three days of CSF drainage at 10mls/hour. All tests were undertaken before and after drainage. Participants were classified as responders or non-responders to CSF drainage by an expert neurologist. Demographic and tests results were similar between the two groups at baseline. All patients with stable tests scored were labelled as non-responder's. In responders, TUG time was shown to improve by 15.69 seconds ($p< 0.05$), and Tinetti scores improved by 3.21 points ($p< 0.001$). Interestingly, Tinetti balance scores were shown to have significant improvement in responders after drainage. To date, this is the only evidence related to balance changes after CSF drainage. The Tinetti assessment and TUG therefore appear useful in identifying potential responders to CSF drainage.[11]

The efficacy of the TUG has been questioned by Kubo who used the TUG together with cognitive testing to determine the reliability and validity of an iNPH grading scale.[65] Of the 38 patients included in the study, no significant differences in measures of TUG between patients who responded to shunting and those who did not was found. While TUG scores tended to be higher in the 14 shunted patients after the CSF TT, the results were not statistically significant.[65] Analysis of TUG results was not the primary aim of this study and with no reported power calculations related to TUG analysis, extrapolation of results is difficult. A possible explanation proposed by Kubo was the TUG is only a measure of walking speed and not fluency of movement, and compared to the proposed iNPH scale, was not as specific in its ability to identify gait changes. However, this explanation is not supported by other authors who have demonstrated identifiable change of TUG results in iNPH after drainage.[11]

Efficacy of computer assisted gait analysis has been explored and demonstrated using the GAITRite portable walkway system.[18] Twenty-eight patients underwent analysis via the GAITRite system after three days of ELD. Fifteen patients underwent shunting in whom statistically significant improvements were reported in gait velocity, double support time and cadence. After shunt insertion all measured

gait variables had significantly improved. However, the commercial links of the author to the system, the equipment space requirements and cost of such a system limits its widespread use in the clinical setting.

The 10m walk test has been used repeatedly as a measure of gait for iNPH. Rarely has it been used in isolation as an assessment, rather being combined with various scales.[15,39,55,65] Boon used the 10m walk test time combined with step count and walking quality score to quantify the extent of gait abnormality.[39] Individual time and step results were not reported, only combined gait scores, preventing analysis of 10m walk test results in isolation. Virhammer used the 10m walk test in 40 patients undergoing a CSF TT. Of the 24 responders to the CSF TT, a mean improvement of 5.4 seconds occurred with a mean decrease of six steps being taken over the course. [50]

Due to their objectivity and repeatability, the validation of tests such as the TUG and 10m walk test as predictors of CSF TT response is warranted. [50] Argument might also be made for the inclusion of objective balance assessments such as the Tinetti or other balance assessments since they have a proven ability to identify and assess balance and gait dysfunction commonly found in patients with iNPH.[11,18]

3.9 The physiotherapists' role in managing patients with iNPH

Since physiotherapists have expertise in the assessment and management of movement disorders, they are called upon to undertake assessment of patients with iNPH. [11] Typically, physiotherapists assess patients before and after CSF TT to determine any improvements in the patient's parameters of gait and balance. Physiotherapists have trained expertise in gait analysis and are uniquely qualified to accurately measure changes in gait and balance following CSF TT.

3.10 Scope for future research

While research has been performed validating predictive balance and gait assessment instruments in patients undergoing ELD, no research has looked at validating the instruments' use as predictors of success in patients with iNPH prescribed to undergo the CSF TT. Given the correlation between CSF drainage and shunt insertion it could be postulated that any measured improvement in a patients gait following CSF drainage might translate into improvements following shunt insertion. Thus, using validated measures to assess gait and balance outcomes following CSF drainage may assist in the prediction of a positive response to shunt insertion. Establishing the predictive ability of such measures might greatly enhance the determination of patients' suitability for shunting.[15] The current lack of evidence into the extent and existence of balance disturbance within this patient cohort would also indicate the need for further research into this area.

3.11 Conclusion

iNPH is confounded by a number of diagnostic and management dilemmas. While general consensus exists with regards to diagnostic features and management options, stringent evidence is lacking. The benefit of upper limb testing in assessment for CSF TT response at this stage appears inconclusive with further determination of validated assessments required. There is clear identification of gait abnormalities present in iNPH and clear links between gait improvement after CSF drainage and improvement after shunting. Further research is required into identification of balance disturbances in iNPH and the efficacy of balance testing. Evidence is lacking regarding the extent to which gait improvement must occur after the CSF TT to infer a likely response to shunting. Due to the intrinsic nature of gait abnormalities associated with iNPH, instruments that measure gait and balance commonly used by physiotherapists have the potential to provide valid assessments. While a stronger emphasis might be placed on measured gait improvements as a prognostic tool, such instruments should be assessed for their validity and predictive value in patients prescribed CSF drainage as precursor to shunting.

Table 3.3 Assessment tools which could be used to assess physical responses in iNPH

Assessment tool	Information
Berg Balance Test [72]	14 item balance assessment score out of 56 Validated in stroke
Patient Orientated Mobility Assessment (Tinetti)[69]	2 part assessment scored out of 28 Gait component score of 16 Balance component score of 12
10m walk test [73]	Time required to walk 10 m distance Validated in ABI, MS, Stroke, Falls population
Timed up and Go (TUG)[74]	Time required to rise from chair with arms walk 3 m around a cone and return to chair Validated in geriatric and stroke population

Chapter 4 Gait and balance measures can identify change from a cerebrospinal fluid tap test in idiopathic normal pressure hydrocephalus

This chapter has been published in *Archives Physical Medicine and Rehabilitation*. [75]

4.1 Synopsis

The CSF TT has been consistently utilised as a supplemental test to determine the suitability for surgery for iNPH. A plethora of outcome measures can potentially be utilised to identify if improvements in a patient's gait, balance and mobility have occurred from CSF drainage. However, the question of what measures should be utilised has never been investigated in detail. Similarly, identification of what constitutes a genuine response on these measures has not been determined.

The previous chapter of this thesis summarized the available evidence pertaining to measures discussed in the literature related to the CSF TT. Furthermore, some work has been attempted to validate standardised outcome measures in other forms of CSF drainage for identification of shunt responsive iNPH. This research has relied on the use of commonly used outcome measures which are regularly used clinically due to their widespread, easy and simple application in a clinical environment.

Based on the evidence presented in the previous chapter and current clinical practices implemented at the facility at which this research was completed, an evaluation of a battery of gait andbalance measures was undertaken to identify the ability of these tests to identify if they could be used to identify change in patients undergoing a CSF TT for consideration of surgery for iNPH.

4.2 Abstract

Objectives: To identify in patients with idiopathic normal pressure hydrocephalus (iNPH) undergoing a cerebrospinal fluid (CSF) Tap Test (TT) for consideration of a ventricular peritoneal shunt: 1. Gait and balance measures which identify symptom change 2. Differences present between pre and post CSF TT scores between patient's classified responders and non-responders 3. Ability of patients with iNPH to accurately quantify change in their gait and balance symptoms from a CSF TT.

Design: Prospective observational study. Post CSF TT assessment was completed 2-4 hours post.

Setting: Tertiary referral neurological and neurosurgical hospital.

Participants: 74 patients with iNPH receiving a 30mls CSF TT for consideration of a VP shunt.

Interventions: Patients underwent a battery of gait and balance measures pre and post CSF TT and indicated their perceived change on a global rating of change (GRC). Patients deemed to improve and offered VP shunt insertion by a neurologist or neurosurgeon were labelled responders.

Main Outcome Measures: Performance Oriented Mobility Assessment (Tinetti), Berg Balance Scale (BBS), Timed Up and Go (TUG), 10m Walk Test (10MWT), GRC.

Results: 40 patients were classified responders, 34 non-responders. Significant differences were identified for responders: Tinetti (3.88 points), TUG (3.98 seconds), 10MWT (0.08m/sec) and BBS (5.29 points). Significant differences were found for non-responders for the Tinetti (0.91 points) and BBS (2.06 points). Change scores for responders and non-responders were significantly different for all tests between responders and non-responders. GRC scores for gait (+2 for responders, 0 for non-responders) and balance (+2.5 for responders, 0 for non-responders) were both significantly different.

Conclusions: The Tinetti, BBS and TUG can identify change in patients undergoing a CSF TT for iNPH. Patients appear to be able to accurately identify if change has occurred.

4.3 Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a reversible form of hydrocephalus presenting with a triad of symptoms comprised of incontinence, gait ataxia and cognitive deficits.[10] This description has formed the basis of iNPH diagnosis for decades, but has since been expanded to include balance and upper limb dysfunction.[6,9,19] Idiopathic normal pressure hydrocephalus differs from other forms, in that no obstruction to cerebrospinal fluid (CSF) flow is identifiable and, as such, it is described as a communicating hydrocephalus.[5] Since first described, treatment has remained unchanged. The gold standard of surgical management for all forms of hydrocephalus involves the insertion of a ventricular peritoneal (VP) shunt to drain excessive CSF. [6,8,19] Determining the suitability of surgical management is compounded by difficulty in diagnosing iNPH which is often done by exclusion of other conditions.[6,17,38] Often patients with provisionally diagnosed Parkinson's Disease, Alzheimer's disease, vascular dementia or musculoskeletal diseases who fail to respond to treatment undergo further examination to identify an alternate diagnosis.[6,25] However, delayed diagnosis may result in disease progression to a point where treatment is no longer effective. To identify who would benefit from surgery, supplemental tests mimicking a VP shunt have been developed. [8,24] Techniques such as external lumbar drainage (ELD) and the CSF tap test (TT) are based on the rationale that symptom improvement from temporary CSF drainage should result in symptom improvement with VP shunt insertion. While ELD requires patients to undergo prolonged bed rest of 3 to 5 days duration requiring hospital admission, the CSF TT is a simpler procedure and can be completed in an outpatient environment.

The CSF TT is commonly used and involves the removal of 30-50mls of CSF via lumbar puncture.[25,26,50] Patients are assessed with a range of tests prior to, and after a CSF TT, to identify symptom improvement. Physiotherapists are routinely involved due to their expertise in gait and balance assessment.[11,15,62] Evidence supporting specific outcome measures assessing response to the CSF TT is sparse. Apart from the 10m walk test, regularly utilised in iNPH studies, no other measures are routinely reported.[11,50] Likewise, the degree of change in patient symptoms that constitutes a positive

response to the CSF TT has not been established. This results in subjective, inconsistent interpretation of response.[6,15,25] The CSF TT is consistently reported to have high positive predictive value for predicting post VP shunt outcome but poor negative predictive value limiting its ability to exclude patients who will not improve from VP shunt insertion.[22,50] One contributing factor to this may be the lack of consistent application of outcome measures to measure response.

Previous research has determined the validity of several balance and gait outcome measures to identify change from ELD.[11] Feick et al identified the Tinetti Performance Oriented Mobility Assessment (Tinetti) and Timed Up and Go (TUG) could identify significant change in patients undergoing ELD over five days with patients deemed to have responded to the procedure demonstrating significant improvement in gait and balance parameters compared to non-responders. No work of this nature has been completed for the CSF TT despite its extensive clinical use.

This study sought to address three research questions: 1. Which gait and balance outcome measures can identify change in gait and balance symptoms of patients with iNPH undergoing a CSF TT? 2. Are differences present between pre and post CSF TT scores between responders and non-responders? 3. Can patients with iNPH accurately quantify change in their gait and balance symptoms as a result of a CSF TT?

4.4 Methods

Design

This prospective study of 74 patients was conducted in a tertiary referral neurological and neurosurgical inpatient facility between June 2013 and December 2016. Patients accepted into the study were admitted for investigation of iNPH and scheduled for a lumbar puncture or Rickman's reservoir CSF TT under either a neurologist or neurosurgeon. This study was approved by the Hunter New England Human Research Ethics Committee, reference: 13/06/19/4.02.

Participants

Diagnosis of iNPH was made by the admitting medical officer (AMO); a neurologist or neurosurgeon, in accordance with international guidelines.[6,44] All patients admitted for a CSF TT were screened for eligibility. Informed written consent was sought prior to undergoing any pre CSF TT testing.

Patients were considered for inclusion in the study if they met the following criteria:

- Undergoing a CSF TT for the consideration of a VP shunt for management of iNPH
- Aged over 55 years in accordance with international guidelines on diagnosis and treatment
- Ventromegaly present on CT or MRI imaging with Evans index>0.3 (the ratio of the width of the frontal horns of the lateral ventricles and the maximal width of the internal diameter at the skull)[8]

Exclusion criteria were as follows:

- Patients aged under 55 years
- Unable to ambulate 10m with an assistive device
- Unable to provide informed consent, or no next of kin who could on their behalf

The use of assistive devices was permitted.

Tap test intervention

The CSF TT was performed by the admitting neurologist/ neurosurgeon by either a lumbar puncture or drainage of an implanted Rickman's reservoir. Each CSF TT aimed to drain 30mls of CSF. Patients were reviewed one to four hours post CSF TT by a physiotherapist involved in patient clinical care. This physiotherapist completed over 98%(71 patients) of testing procedures with the remaining 2%(3

patients) completed by another physiotherapist in their absence. The same physiotherapist administered pre and post CSF TT assessments.

One neurosurgeon chose to insert Rickman's reservoirs in lieu of a lumbar puncture due to their longstanding clinical practice. Rickman's reservoirs are a subcutaneous CSF reservoir linked to the lateral ventricles by a catheter. CSF volumes drained and the latency between the procedure and review post CSF TT were the same irrespective of the drainage technique.

Outcome measures

Based upon previous investigation of the CSF TT and ELD, in addition to current clinical practice, a battery of tests were utilised to identify change.[62]

1. Berg Balance Scale(BBS)
2. Performance Oriented Mobility Assessment(Tinetti)
3. Timed Up and Go(TUG)
4. 10 metre walk test(10MWT)

Each of these standardised measures has been described extensively, utilised widely, and validated in multiple patient cohorts.[61,76,77] All tests have demonstrated excellent interrater and intrarater reliability.[78,79]

The TUG times how long it takes to rise from a chair, walk 3 metres and return. The 10MWT measures the time taken to walk 10 metres from a moving start.[61,80] The BBS is a 14 point scale assessing static and dynamic balance scored out of 56 points. The Tinetti consists of a balance section assessing 9 items scored out of 16 points along with a gait section assessing 8 items scored out of 12 with a combined score of 28 points.[78,79]

Following the CSF TT, patients were asked to indicate whether they thought there was change in their balance and gait symptoms using a global rating of change (GRC) scale. This is a visual scale with ratings ranging from -5 to +5, whereby -5 is labelled completely worse, 0 labelled no change and +5 labelled complete improvement.[81] Separate score sheets documented perceived changes in gait and balance. Patients were instructed complete improvement should mean their symptoms had resolved while completely worse meant their symptoms were unmanageably worse.

Determination of response

Results of gait and balance testing were provided to the AMO along with radiological examination, cognitive examination, and patient reported levels of improvement. These were utilised by the AMO to determine response status and decide whether surgery should be offered. Five neurosurgeons and eight neurologists all with between 5 and 30 years specialist experience acted as AMO for participants. The AMO after reviewing all available results was responsible for determining the significance of improvement seen across all test batteries. Patients were categorised as responders where surgery was offered, regardless of whether surgery was accepted or declined. Patients not offered surgery were categorised as non-responders.

Data analysis

Patients were dichotomised into responders and non-responders for analysis. Within-group analysis for responders and non-responders was undertaken to determine the significance of change within groups with regard to pre and post CSF TT scores. Analysis of change scores to determine if differences were present between responders and non-responders was completed. Significance levels were set at 0.05 for all tests. Spearman's correlation was utilised to calculate correlation coefficients between GRC scales and all outcomes measures. Gait GRC scores were correlated with TUG, Tinetti gait sub-

score (Tinetti gait) and 10MWT while balance GRC scores were correlated with the Tinetti balance sub-score (Tinetti balance), Tinetti and BBS. As the Tinetti balance sub score is the largest contributor, the Tinetti correlation with balance GRC was used.

Data was analysed using Stata 13 (StataCorp Tx). Skewness-kurtosis analysis was completed on all data to assess normality. TUG data was found to not be normally distributed, hence Mann Whitney and Wilcoxon sign rank tests were utilised. T-tests were used for all other data. Chi square tests analysed differences in gender and triad symptoms between groups.

Sample size for the included outcome measures were calculated using established minimal detectable changes (MDCs).[61,76] A MDC for the TUG was selected from a Parkinson's population in the absence of reported MDC in iNPH. The TUG required the highest participant number to identify a statistically significant difference with an MDC of 3.5 seconds, and was used for determining recruitment numbers. Based upon a significance value of 0.05 and 80% power, a sample size of 74 patients was required.

4.5 Results

Participants

Seventy-seven patients were invited to participate. One patient declined participation and two patients were excluded following a misdiagnosis of iNPH. Seventy-four patients completed pre and post CSF TT testing.

Table 4.1 provides demographic and symptom information. No significant differences were present between responders and non-responders for the presence or number of triad symptoms. Differences in age and gender between groups were not statistically significant.

Table 4.1 Patient demographics

	Study Population	Responder (N=40)	Non-responders (N=34)	P value
Age(years)*	75 (68,80)	75 (72,82)	73.5 (64,80)	P=0.20
Gender (M/F)	47/27	24/16	23/11	P=0.39
Symptom duration (Months)	9 (6,12)	9 (6,12)	9 (6,24)	P=0.30
Time to post CSF TT assessment(hours)*	2(1.5,2)	2(1.5,2)	2 (1.5, 2.5)	P=0.45
CSF Volume drained(mls)†	29.54 (4.31)	28.94 (5.47)	30.24 (2.17)	P=0.20
Percent of triad present (Gait/Cognition/ Incontinence)	81%/70%/37%	90%/73%/35%	88%/68%/41%	P=0.72
Number of triad symptoms present 3/2/1	36%/36%/28%	36%/41%/23%	36%/30%/33%	P=0.17

* Median (interquartile range), †mean (standard deviation)

Tap Test Type

Nine patients received a CSF TT via Rickman's reservoir. No significant differences were present for demographics or test scores between CSF TT completed by lumbar puncture or Rickman's reservoir. An average of 29.54 ml of CSF was drained with no between group difference. Median time until post CSF TT review for both groups was 2 hours.

Pre and Post Tap Test Scores

Table 4.2 provides test results for responders and non-responders. Sub-scores of the Tinetti (balance and gait) are presented. Significant differences were identified between pre and post scores for

responders on all tests. For responders, the TUG identified median change of 3.98 seconds. Tinetti balance showed a mean change of 2.25 points and the Tinetti gait 1.52 points. The Tinetti demonstrated a mean change of 3.88 points and the BBS 5.29 points. The 10MWT showed a mean change of 0.08m/ sec. Three tests identified significant pre and post differences for non-responders: the Tinetti Gait (0.44 points), Tinetti (0.91 points) and BBS (2.06 points). No between group differences existed for any pre CSF TT scores. Significant between group differences were present in post CSF TT scores for Tinetti balance (p=0.01) and Tinetti (p=0.02).

Significant differences were present for change scores for all outcome measures between responders and non-responders, the Tinetti (p<0.01 CI -4.05, -1.88), Tinetti Balance (p<0.01 CI -2.80, -1.17), Tinetti gait (p<0.01 CI -1.71, -0.43), TUG (p=0.02 CI -9.47, -0.21), BBS (p<0.01 CI-4.77, -1.51) and the 10MWT (p=0.05 CI 0, 0.15).

Figure 4.1 compares Tinetti and BBS change scores by response, Figure 4.2 TUG change scores by response, and Figure 4.3 10MWT change scores by response.

Figure 4.1 Change scores by response for Tinetti and BBS

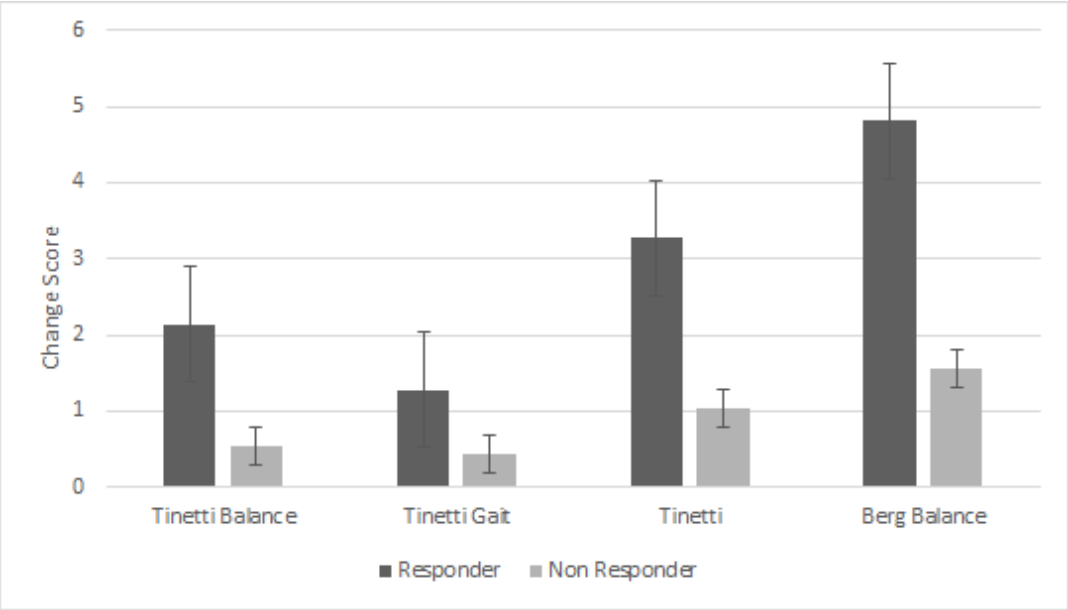


Figure 4.2 Change scores by response for TUG

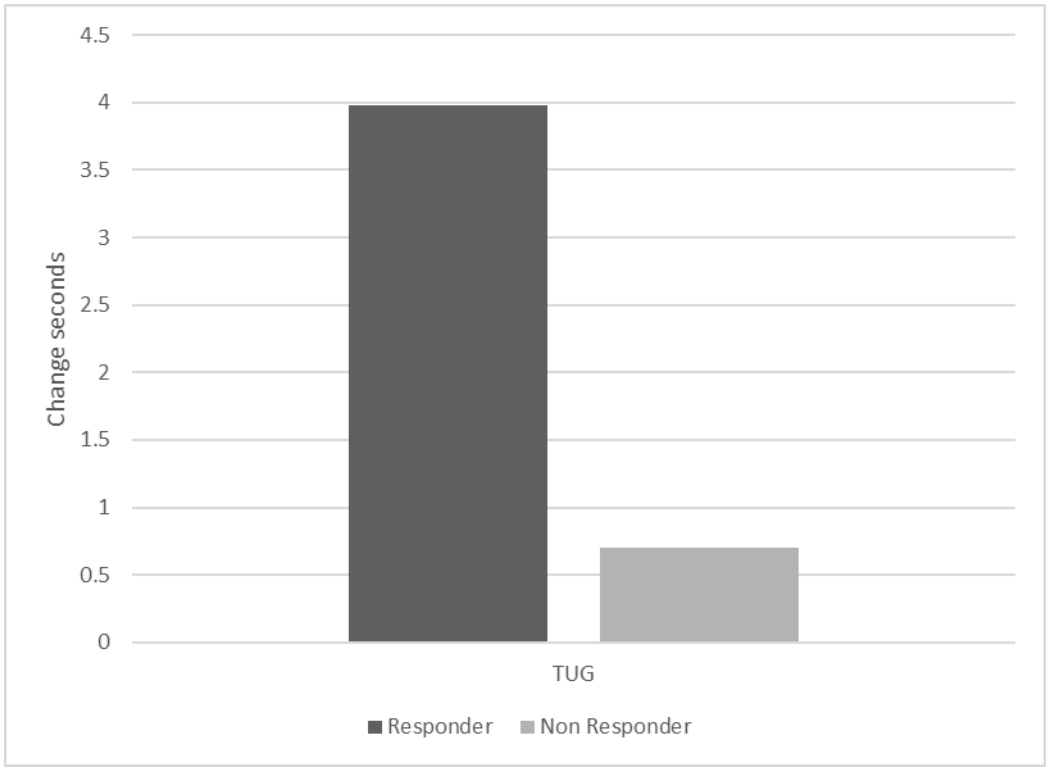


Figure 4.3 Change scores by response for 10MWT

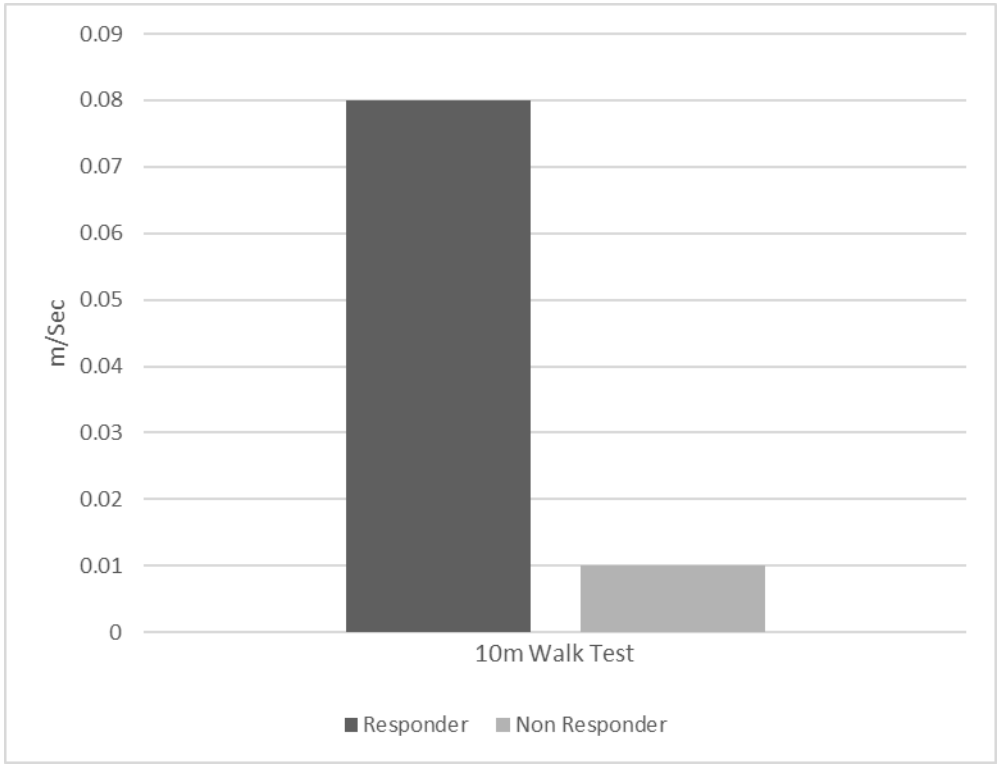


Table 4.2 Testing scores pre and post CSF TT for all testing parameters

Test	Responder			Non-responder			P Value difference pre CSF TT score by response#	P value difference post CSF TT score by response
	Pre CSF TT Median (IQR)/ Mean(SD)*	Post CSF TT Median (IQR)/ Mean(SD)	P value difference pre/post** (95% CI)	Pre CSF TT Median (IQR)/ Mean(SD)*	Post CSF TT Median (IQR)/ Mean(SD)	P value change pre/post** (95% CI)	(95% CI)	(95% CI)
Timed Up and Go (Sec)	18.90 (13.3, 23.10)	14.92 (11.65, 21.90)	**P<0.01** **(0.54, 8.18)**	17.10 10.60, 29.60)	16.4 (10.20, 28.30)	P=0.69 (-3.19, 2.02)	P=0.92 (-7.05, 8.32)	P=0.40 (-0.88, 12.05)
Tinetti Balance	10.20 (2.98)	12.45 (4.06)	**P<0.01** **(-2.99, -1.81)**	10.14 (4.11)	10.56 (4.08)	P=0.15 (-1.00, 0.16)	P=0.97 (-1.70, 1.60)	**P=0.01** **(-3.60, -0.47)**
Tinetti Gait	7.38 (2.35)	8.90 (2.18)	**P<0.01** **(-2.03, -1.02)**	7.59 (2.65)	8.03 (2.76)	**P=0.02** **(-0.80, -0.09)**	P=0.71 (-0.95, 1.37)	P=0.13 (-2.02, 0.27)
Tinetti	17.65 (4.72)	21.53 (4.11)	**P< 0.01** **(-4.68, -3.07)**	17.74 (6.42)	18.65 (6.51)	**P=0.01** **(-1.64, -0.18)**	P=0.95 (-2.50, 2.67)	**P=0.02** **(-5.37, -0.39)**

10 Metre Walk (m/sec)	0.68 (0.28)	0.76 (0.26)	**P<0.01** **(-0.14, -0.02)**	0.79 (0.43)	0.80(0.26)	P=0.63 (-0.05, 0.03)	P=0.20 (-0.06, 0.28)	P=0.67 (-0.13,0.20)
Berg Balance Scale	35. 39 (8.57)	40.68 (7.69)	**P< 0.01** **(-6.43, -4.15)**	36 (11.81)	38.06 (12.33)	**P<0.01** **(-3.36, -0.77)**	P=0.75 (-4.30, 5.51)	P=0.28 (-7.47, 2,23)

* Timed Up and Go reported Median (IQR) all other tests mean (SD)

Bold text indicates statistically significant result

** Non-parametric testing for Timed Up and Go

Non-parametric testing for Timed Up and Go

Global Rating of Change scores

Table 4.3 presents GRC scores by response. Responders indicated a median balance change of 2 and 2.5 for gait. Non-responders indicated a median change of 0 for GRC for both balance and gait. Between group GRC change score differences were significant.

Table 4.3 Global perceived change scores

Global Rating of change	Overall	Responder	Non-responder	P value
	Median (IQR)	Median (IQR)	Median (IQR)	(95% CI)
Balance	1 (0,2.5)	2 (1,3)	0 (0,2)	**P<0.01**
				(-1.83, -0.56)
Gait	1 (0,3)	2.5 (1,3.5)	0 (0,1)	**P<0.01**
				(-2.22, -0.82)

Bold text indicates statistically significant result

Change score correlation

Correlation scores for all tests were statistically significant (Table 4.4). Subgroup correlation by response status showed no significant correlations for any test for responders except the BBS (r=0.35). Non-responders showed significant correlation for the TUG (r=0.36), Tinetti Balance (r= 0.34), Tinetti (r=0.42) and BBS (r=0.48).

Table 4.4 Correlation scores between test change scores and global rating of change scores

Test	Overall	Responder	Non-responder
TUG	**r=0.33 p<0.01**	r=0.21 p=0.23	**r=0.36 p=0.03**
Tinetti Balance	**r=0.32 p<0.01**	r=-0.03 p=0.84	**r=0.34 p=0.05**
Tinetti Gait	**r=0.37 p<0.01**	r=0.32 p=0.07	r=0.24 p=0.16
Tinetti	**r=0.47 p<0.01**	r=0.31 p=0.07	**r=0.42 p=0.01**
BBS	**r=0.50 p<0.01**	**r=0.35 p=0.04**	**r=0.48 p<0.01**
10MWT	**r=0.37 p<0.01**	r=0.23 p=0.19	**r=0.37 p=0.03**

Bold text indicates statistically significant result

4.6 Discussion

This study provides evidence that several gait and balance outcome measures are useful in detecting change from a CSF TT in patients with iNPH. Significant differences were present between responders and non-responders for the Tinetti, BBS, TUG and 10MWT for pre and post CSF TT assessments. Responder change scores for all tests, with the exception of the 10MWT, represent scores equal to or larger than established MDCs for these tests, supporting the inference of genuine change.[61,76,77] Interestingly, significant change was identified for non-responders for the Tinetti Gait, Tinetti and BBS. It was deemed that as the change scores for non-responders were well below established MDCs, while statistically significant, they are not clinically meaningful.

The Tinetti has been previously shown to identify change from ELD and our results suggest that it can also identify change from a CSF TT. Change scores reported from ELD for the Tinetti of 3.21 points are consistent with findings in this study.[11] A four point mean change for responders is equal with established MDCs for elderly individuals.[77] Comparison of pre and post test scores to normative values suggests that there was marked gait and balance impairment in this group of patients.[82] The magnitude of change seen on the Tinetti would therefore support the inference of genuine change being measured by this instrument.

Non-responder change scores for the Tinetti of less than 1 point could be argued to fall within measurement error. Significant between-group differences for the Tinetti post CSF TT scores, suggests those with a higher score post CSF TT can be identified as likely to be responders. This was also true for the balance sub-score. These findings support the ability of the Tinetti to detect response from a CSF TT. When the components of the Tinetti are considered individually, both sub-scores show significant ability to identify change for responders and non-responders. Again, the clinical relevance of change for non-responders can be questioned with mean change scores well below one point, where only full and not half points can be attributed in these tests.

It is only in recent years that balance impairment has been recognised as a significant component of the phenotype of iNPH.[22] The results from this study confirm that balance is affected in patients with iNPH and change can be identified using the BBS. Mean change scores for responders and non-responders were both significant, however, similar to the Tinetti, non-responder change scores were below established MDCs indicating an absence of clinical significance.

The TUG is a simple, frequently used test of gait. Minimal equipment requirements, established validity, reliability and normative values, endorse its frequent clinical utilisation.[80] Finding statistically significant change for responders supports the use of this test as an outcome measure in iNPH. Non-responder change scores were neither statistically or clinically significant, further reinforcing the utility of the TUG to discriminate response.

The 10MWT is the most commonly reported test utilised in iNPH research. As with the TUG, the 10MWT is a simple test requiring only a stop watch and walkway to perform. Comparison of 10MWT times to normative values suggests the study sample had moderate gait impairment on admission regardless of responder status.[83] Although the magnitude of change for responders was statistically significant in this sample, test values were below established MDC's for both response categories suggesting that the 10MWT may not be sufficiently sensitive to identify change following a CSF TT.

Participant's perception of change following a CSF TT allows quantification of patient's perception of change in their gait and balance. This would suggest that patients appeared to be able to accurately identify when change had occurred after a CSF TT; however, GRC change scores were only weakly correlated to test results. The BBS was the only test to reveal a significant correlation for responders. For non-responder's correlation scores were slightly stronger, and significant for all tests except the Tinetti Gait sub-score. This would suggest that patients appeared to be able to accurately identify when change had occurred after a TT, however, they were unable to either recognise or quantify the extent of this change.

This study utilised a large number of outcome measures to attempt to quantify change. The number of outcome measures that need to be completed to quantify change has not been explored in this study. It is likely that a smaller number of measures would be able to quantify change from a CSF TT. Future work should aim to identify what level of change on these measures is meaningful clinically, and how many outcome measures are required to accurately identify when change has occurred subsequent to a CSF TT. This may facilitate further research to improve the prognostic ability of the CSF TT to predict improvements post VP shunt insertion.

Strengths of this study include the tests utilised are readily available, require minimal training, and are routinely used. The reported use of Tinetti, 10MWT and TUG in ELD supported their inclusion in the assessment following the CSF TT. This study provides further support for the use of these tests to identify change in performance occurring as a result of a CSF TT for iNPH. Sample size calculations were based on the TUG, which may explain the presence of statistically significant yet small magnitude change scores in non-responders for the Tinetti and BBS.

Study limitations

A potential limitation to this study is the ability for differences in pre and post scores to be influenced by a learned effect due to the short period of time between completing pre and post testing. While this cannot be excluded from this study design, comparison of change scores for the Tinetti in this study are consistent in magnitude to change scores reported in ELD studies (3.88 vs 3.21 in ELD for responders and 0.9 vs 0.7 in ELD for non-responders)[11] suggesting that a confounding effect has not occurred. The determination of response to the CSF TT was based on expert medical opinion. This decision, while made by highly qualified medical specialists, may impact the reproduction of these results as there is currently no universally accepted criteria to determine response from these measures in this population.

4.7 Conclusion

Statistically and clinically significant change resulting from a CSF TT for patients with iNPH can be detected on assessment of the TUG, Tinetti, and BBS. The 10MWT does not appear to be sensitive to identifying change with change scores below established MDCs. The clinical application of these tests can support clinicians to identify the presence of change from a CSF TT and therefore the suitability of surgical intervention. Patients' identification of changes in their symptoms are consistent with the presence of change identified on objective testing and can be confirm whether change in symptoms from a CSF TT has occurred.

Chapter 5 Cognitive and upper limb symptom changes from a tap test in idiopathic normal pressure hydrocephalus

This chapter has been accepted for publication with Clinical Neurology and Neurosurgery[84]

5.1 Synopsis

In addition to its use in assessing gait and balance changes, the CSF TT is also utilised to assess for change in relation to cognitive status. Although changes in cognition are regularly reported as more inconsistent than improvements in gait, and the presence of cognitive decline is indicative of a poor response to shunting, cognitive testing remains common when assessing response to the CSF TT.

Links between upper limb function and executive function have been drawn by multiple authors.[11,22,71] Limited research has been completed assessing upper limb function changes resulting from CSF drainage. Based on this, investigation of upper limb function, along with cognitive changes is warranted.

The question of which assessment tools should be used to assess these outcomes is difficult to answer with even less prior research on these symptoms when compared to gait and balance. To investigate this, we once again used a combination of evidence from available research and current clinical practice to identify a battery of standardised assessment tools to analyse cognitive and upper limb function changes from a CSF TT. This chapter presents the findings of this analysis.

5.2 Abstract

Objectives: To determine which cognitive and upper limb assessments can identify change in patients undergoing a Cerebrospinal fluid (CSF) tap test (TT) diagnosed with idiopathic Normal Pressure Hydrocephalus (iNPH).

Patients and Methods: Prospective observational study of 74 iNPH patients undergoing a CSF TT for consideration of a ventricular peritoneal shunt. Patients who were offered surgical intervention were classified as responders. Patients were assessed with a battery of cognitive and upper limb assessments prior to and following a CSF TT. The Timed up and go cognition (TUG-C), Montreal Cognitive assessment (MoCA) and 9-hole peg test were utilised.

Results: 40 patients were classified responders. Significant differences were identified for responders for the MoCA (0.62 points) and TUG-C (-6.02 secs). Only the executive function and orientation sub scores of the MoCA showed significant changes for responders. The 9 hole peg test mean change of 4.33 seconds for responders was not significant. Non-responder change scores for the MoCA (0.22 points), TUG-C (0.3 seconds) and 9 hole peg test (2.58 seconds) were not significant.

Conclusion: The TUG-C has the potential to identify change in patients resulting from a CSF TT. While statistically significant change was found for the MoCA, a mean change of less than 1 point on this scale is unlikely to be clinically relevant. Similarly, the 9 hole peg test cannot be endorsed as an assessment tool for identifying changed performance in iNPH.

5.3 Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition where patients present with a triad of symptoms of high level gait disorder, incontinence, and cognitive deficits.[8] A neurosurgical procedure, insertion of a ventricular peritoneal (VP) shunt, represents the gold standard treatment.[6,26] This implanted surgical device is designed to divert cerebrospinal fluid (CSF) from the brain ventricles into the peritoneal space. However, not all patients diagnosed with iNPH will benefit.[9] To identify who may benefit supplemental tests have been developed to mimic a shunt.[8,24,26,54] The CSF tap test(TT) aims to temporarily drain CSF.[50] The CSF TT drains between 30 and 60mls of CSF and patients are assessed prior to and after CSF drainage to determine if changes in symptoms, typically gait and cognition, have occurred.[26,50]

iNPH symptoms often overlap or coexist with Parkinson's disease(PD), Alzheimer's disease (AD), or frontal dementia.[8,50] Determining iNPH cognitive deficits opposed to co-existing cognitive deficits can prove difficult.[22,85,86] Subtle differences have been demonstrated between iNPH and AD with frontal lobe dysfunction disproportionately severe in iNPH and memory impairment distinctly mild compared to matched AD sufferers. [22,64,85] Idiopathic Normal Pressure Hydrocephalus suffers score better orientation and delayed recall testing compared to AD patients but worse on arithmetic and digit symbol substitution tests.[85] Generally the cognitive deficits of iNPH are isolated to executive function impairment.[22] These differences facilitate the ability to assess for cognitive change from a CSF TT.

Extensive evidence supports the prognostic efficacy of the CSF TT to predict positive response post insertion of a VP shunt. [9,54,87,88] However, what degree of change constitutes a positive response and which tests quantify the change resulting from a CSF TT is not clear. Cognitive examination is routinely undertaken to identify patients who may benefit from VP shunt insertion.[6,22]

A previous study investigated the Cognitive Assessment of Minnesota (CAM) to determine if changes could be identified after external lumbar drainage (ELD), an alternative CSF drainage technique, showing it was sensitive in detecting differences between responders and non-responders to surgical

intervention.[11] The Montreal Cognitive Assessment (MoCA) is a cognitive examination testing similar domains to the CAM which has been suggested for use in the iNPH population based on its use in other forms of dementia. [89] The MoCA is valid in assessing mild cognitive impairment.[90]

Additionally counting backwards from 20 has been evaluated to assess executive function in patients undergoing VP shunt insertion.[91] Counting backwards has been shown to be accurate, valid assessment in iNPH. The Timed Up and Go Cognition (TUG-C) is a test combining a serial counting backwards test with a timed walking task. A combination of the Timed Up and Go with a serial counting backwards task could have potential to aid in identification of surgical candidates. The Timed Up and Go has demonstrated an ability to identify responders v non responders to the tap test previously.[75]

Upper limb tests used to measure CSF TT response have been reported in large international iNPH trials.[22] The efficacy of upper limb assessments to detect changes in upper limb performance has been shown by a small body of evidence.[71] Upper limb function testing, using line drawing and tracing tasks, has been investigated to identify change from a CSF TT.[71] The authors suggest that simple upper limb tasks may identify CSF TT responders in addition to traditional gait based assessments.[71] Patients completed a line tracing task before and after a CSF TT. Responders were noted to have an average reduction of 12% in time to complete a tracing task.[71] The 9 hole peg test assesses dominant hand function by measuring the time taken to individually pick up 9 pegs, place them into a 9 slot peg board and remove them again.[92] The 9 hole peg test has been evaluated previously in iNPH and is valid in identifying upper limb dysfunction in PD.[11,92] The 9 hole peg test has been evaluated unsuccessfully previously in ELD. It was not able to identify improvements in upper limb function from 5 days of ELD.
[11]

Attempts to identify CSF TT responders varies substantially clinically and within research as many different assessment tools are utilised. Confounding this, no research has focussed on defining meaningful change by which a positive response can be identified. Currently, arbitrary values of 5 or 10% improvement are listed as signs of positive response.[22] This study sought to answer two

questions: 1. Identify cognitive and upper limb assessments which can detect change resulting from a CSF TT in patients with iNPH.

2. Identify differences present between patients who respond and do not respond to a CSF TT for cognitive and upper limb assessments.

This information is necessary to streamline and standardise the assessment process currently used by clinicians and to objectively guide decisions regarding patient's suitability to undergo VP shunt insertion.

5.4 Patients and methods

This prospective observational study was conducted in a tertiary referral neurological and neurosurgical facility. Patients admitted to this facility for investigation of iNPH and scheduled to undergo a CSF TT between June 2013 and December 2016 were provided with written information explaining the aims of the study and written consent to participate in the study was sought. This study was approved by the Hunter New England Human Research Ethics committee, reference: 13/06/19/4.02.

Patients were eligible for inclusion in the study if they were admitted for a CSF TT for iNPH, aged over 55 years and diagnosed with Ventromegaly on CT or MRI imaging with Evans index >0.3. Patients were excluded if they could not walk 10m with assistance. Mobility aids were permitted. Patients who were unable to consent to the study or did not have a next of kin available to consent were also excluded. Demographic data was collected from patients and their medical records.

iNPH diagnosis and Pre-Post CSF TT assessment

Diagnosis of iNPH by the admitting medical officer was in accordance with international guidelines on the diagnosis of possible and probable iNPH.[6,44]

The Montreal Cognitive Assessment (MoCA), Timed up and go cognition (TUG-C) and 9-hole peg tests were selected for use based on available research and current clinical practice. The MoCA is routinely used at the participating facility to assess cognitive deficit and was utilised in iNPH prior to the commencement of this study. The TUG-C was selected based on its ability to assess gait and cognitive function.

The MoCA consists of 30 items assessing short term memory, abstraction, executive function, orientation, and language. [93] Three versions of the MoCA exist eliminating learned effect from completing the same test within several hours. Scores below 26 represent mild cognitive impairment and below 21, moderate impairment.[90] The MoCA has been found valid and reliable in PD, AD and cognitive decline.[94] The TUG-C requires patients to rise from a chair, walk 3m, turn around walk back and sit while counting backwards serially from 100. The TUG-C is a multistep process relying on a level of executive function to correctly execute. The TUG-C has been validated in PD and falls patients. [20, 21] The Timed Up and Go has been demonstrated an ability to identify responders v non responders to the tap test previously.[22] The 9 hole peg test is a timed test requiring patients to individually pick up 9 pegs, place them into a board and remove them again.

A physiotherapist and occupational therapist involved in the clinical care of the patient completed the above tests prior to the CSF TT which was conducted by the admitting medical officer (AMO). The assessments were re-administered within 4 hours of the CSF TT by the same occupational therapist and physiotherapist. Different versions of the MoCA were used on pre-and post CSF TT assessment to eliminate potential for learned affect to confound results.

Tap test method

One neurosurgeon inserted Rickman's reservoirs, a subcutaneous CSF reservoir linked to the lateral ventricles by a catheter, to facilitate a CSF TT. Lumbar puncture CSF TT's were completed by all other neurologists and neurosurgeons. Each CSF TT aimed to drain 30mls of CSF.

Determination of response

Gait, balance, radiological examinations, cognitive and upper limb examinations were provided to the AMO. Patients were classified as responders where the AMO determined improvement in symptoms had occurred across all testing parameters and surgical intervention was offered to the patient. Patients not offered surgery were labelled non-responders.

Statistical analysis

Patients were dichotomized by response status for analysis. Pre-post scores were analysed by response status. Pre and post CSF TT scores along with change scores were analysed by response status to determine if differences were present.

Stata 13(Statacorp) was utilised for analysis. Skewness-kurtosis testing on data determined if data was normally distributed. Mann Whitney U and Wilcoxon sign rank tests were utilised to compare all pre post CSF TT data and demographic data except for the MoCA total where paired t tests were utilised. Chi square tests assessed differences between responders and non-responders for gender and triad symptoms. Significance levels for all tests were set at a p=0.05.

Recruitment numbers for this study were based on power calculations for a separate arm of this research investigating gait and balance assessments used in association with the CSF TT.[75] A total of 74 patients were recruited.

5.5 Results

Demographics

Seventy-seven patients were approached, and 76 were recruited as one patient declined involvement. Two patients were later excluded due to a misdiagnosis of iNPH leaving 74 participants enrolled in the study.

Patient demographics have been published elsewhere in detail.[75] The median patient age was 75 and the median duration of symptoms was 9 months. Gait disturbance was the most prevalent triad symptom (81%), followed by cognitive deficits (70%) and urinary incontinence (37%). 36% of patients had all triad symptoms, 36% had 2 symptoms and 28% had 1 symptom.

Tap test type

Nine patients underwent a Rickman's reservoir CSF TT. No significant differences were present between patients who underwent a CSF TT via lumbar puncture of Rickman's reservoir on any test result or demographic parameter. Median time to completing post CSF TT assessment was 2 hours. Median CSF volume drained from patients was 29.54mls, no difference was present between groups (p=0.20).

Pre post CSF TT Scores

Sixty-three patients completed the MoCA, 31 completed the TUG-C and 27 completed the 9 hole peg test. Based on interim analysis results of the MoCA it was identified that additional tests would need

to be evaluated to identify cognitive function change from a CSF TT. As a result, the TUG-C and 9 hole peg test were added to the assessment battery after the commencement of the study. Due to this 31 patients completed the TUG-C and 27 the 9 hole peg test.

Table 1 lists results for responders and non-responders. For responders, statistically significant differences were present for the MoCA (0.48 points) and TUG-C (6.02 seconds). For responders, a median change score of 4.33 seconds on the 9 hole peg test was not significant. Response status could not be determined based on pre CSF TT scores or post CSF TT scores for any tests.

Median non-responder change scores of 0.22 for the MoCA, 0.3 seconds for the TUG-C and 2.50 seconds for the 9 hole peg test were not significant. The MoCA scores of 24 patients regressed on post CSF TT scores. A decline was also seen for eight patients on the TUG-C and 9 hole peg test.

Table 5.1 Test score pre and post TT for all tests

Test	Responder			Non-Responder			P Value difference pre CSF TT score by response*	P Value difference post CSF TT score by response*
	Pre TT Median (IQR)/ Mean(SD)	Post TT Median (IQR)/ Mean(SD)	P value difference pre/post*	Pre TT Median (IQR)/ Mean(SD)	Post TT Median (IQR)/ Mean(SD)	P value change pre/post*		
Timed Up and Go Cognition (Sec) (n=31)	23.40(16.60,26.20)	17.38(12.95, 24.80)	P<0.01	19.22(13.70, 28.08)	19.52(12.68, 21.92)	P=0.63	P=0.42	P=0.80
Montreal Cognitive Assessment (n=63)	18.16(4.98)	18.64(5.51)	P=0.02	19.23(5.17)	19.45(5.22)	P=0.51	P=0.42	P=0.55
9 hole peg test (Sec) (n=27)	36.53(29, 43.40)	32.20(26.50, 39)	P=0.14	34(30.20,36.77)	31.42(30.59, 34)	P=0.51	P=0.76	P=0.90

*Non parametric testing utilised for Timed Up and Go Cognition and 9 hole peg test. Parametric tests used for Montreal Cognitive Assessment

MoCA sub scores

Table 2 summarises MoCA sub scores by response. MoCA sub score analysis by response showed executive function (1 point change) and orientation (1 point change) change scores were statistically significant for responders. The language change score for responders (1 point) was not significant. No change occurred for naming attention, abstraction or delayed recall.

No significant differences were present for non-responders. Executive function and attention sub scores for non-responders decreased by 1 point post CSF TT. No change occurred for naming, language, abstraction, or delayed recall. 0.5 change for orientation was not significant.

Test	Responder			Non-Responder			P Value difference pre CSF TT score by response*	P Value difference post CSF TT score by response*
	Pre TT Median (IQR)	Post TT Median (IQR)	P value difference pre/post*	Pre TT Median (IQR)	Post TT Median (IQR)	P value change pre/post*		
Executive function	2 (1,3)	3 (2,4)	P<0.01	3 (1,4)	2 (2,4)	P=0.61	P=0.28	P=0.94
Naming	3(3,3)	3 (3,3)	P=0.72	3 (3,3)	3 (2,3)	P=0.45	P=0.96	P=0.22
Attention	4(3,6)	4 (2,6)	P=0.95	5, (2,5)	4 (3,6)	P=0.64	P=0.78	P=0.78
Language	1 (1,2)	2 (1,2)	P=0.06	2 (1,2)	2 (1,2)	P=0.85	P=0.30	P=0.97

Abstraction								
	1 (0,2)	1 (0,2)	P=0.19	1 (0,2)	1 (1,2)	P=0.83	P=0.70	P=0.45
Delayed recall								
	1 (0,3)	1 (0,2)	P=0.43	0 (0,3)	0 (0,1)	P=0.32	P=0.38	P=0.28
Orientation								
	5 (5,6)	6 (5,6)	P=0.03	5.5 (4,6)	6 (5, 6)	P=0.74	P=0.94	P=0.54

Table 5.2 MoCA pre and post TT sub scores by response

*Non parametric testing utilised

5.6 Discussion

This study represents the first attempt to quantify the capacity of this battery of cognitive and upper limb tests to identify change resulting from a CSF TT in patients with iNPH. This study evaluated the MoCA, TUG-C and 9 hole peg test to assess changes in cognitive and upper limb performance.

Results for the MoCA are surprising given the established reliability and validity of this test in cognitive impairment.[93] The MoCA has recently been suggested as a test which may be of benefit in neuropsychological testing for iNPH.[89] However, our results would suggest this however is not the case in determining improvement in cognitive function as a result of a CSF TT. Failure of the MoCA to identify cognitive improvement may suggest the timeline to reassessment may not allow for significant cognitive change to occur, or that the MoCA may not be appropriate for application in such a test retest scenario. The MoCA is designed as a brief screening tool by which all domains of cognition may be rapidly assessed. The CAM, which has been shown to identify change from 5 days of ELD, however assesses a wider range of cognitive tasks taking considerably longer to apply than the MoCA. We speculate that the in depth nature of the CAM may be more sensitive in identifying subtle changes which may occur as a result of a CSF TT. Comparison between these two tests across these different CSF drainage methods is however difficult. The difference identified in cognitive deficits between AD and iNPH may also have an impact on the MoCA's ability to detect subtle changes. Mean change for responders, while statistically significant, cannot be considered clinically relevant. A change score of less than one point cannot exclude the possibility of measurement errors and is not measurable in an examination. Significant change in sub scores for executive function and orientation fit known cognitive deficits of iNPH suggesting the utilisation of these sub scores of the MoCA could be beneficial. Again, as the change scores are small (1 point for both) the risk of error cannot be excluded. The lack of change in attention sub scores are surprising with no significant differences present between any pre post or responder/ non responder analysis. Median scores of 4 for responders and 5 for non-responders indicate mild deficits were present in both groups regardless of response status. These however do not appear to be responsive to the CSF TT however. Thirty-eight percent of patients

recorded a declined in their post CSF TT MoCA scores, which was not anticipated as an improvement or no change was expected.

Findings in relation to the 9 hole peg test are consistent with previous research in ELD and iNPH.[11] When the scores for these iNPH patients are compared to normative values it is evident that upper limb deficits are present. Previously proposed rationales for these deficits is the link to decline in executive function and praxis associated with cognitive deficit from iNPH.[71,95] The 9 hole peg test has been evaluated to identify change in ELD without any success. Its simple time efficient application however warranted its evaluation in relation to the CSF TT.[11] Despite a median 4.06 second change this was not statistically significant. It should be noted non-responder median change score of 2.58 seconds is not largely different to responder change score. This is consistent with previous evaluations.[11] The failure of the 9 hole peg test to register significant change should not preclude further evaluation of alternative upper limb examinations in relation to iNPH.

The TUG-C identified change in responders. The construct of the TUG-C evaluating gait and cognitive ability to count backwards while ambulating is supported by previous research of counting backwards and dual tasking as an assessment item for iNPH. Currently no MDC's have been determined for the TUG-C. Based on established MDC's for the Timed up and it would be reasonable to argue a change of 6 seconds would exceed an MDC for the TUG-C. The large difference in change scores between responders and non-responders suggests ability to discriminate responders from non-responders.

A primary strength of this study is the investigation of routinely used clinical tests rendering the findings clinically relevant. Potential limitations include the method of determining response status. Currently no gold standard exists for determining a positive response to a CSF TT. This study is reliant on the expert opinion of consultant Neurosurgeons and Neurologists to determine response. Only one test of upper limb function was considered in this study only allowing conclusions to be drawn on this test alone and not upper limb examination in relation to the CSF TT in general.

This study demonstrates the TUG-C is an effective test for identifying change from a CSF TT. Consistent with the findings from alternate CSF drainage techniques used in iNPH, the use of the 9 hole peg test to measure change is not supported by this research. Small change scores identified by the MoCA for responders, while statistically significant, cannot be considered clinically relevant. Based on this, combined with significant change only being identified in executive function and orientation sub scores, utilisation of the MoCA to identify change from a CSF TT should be reconsidered. Consideration of alternative cognitive examinations examining executive function and orientation should be considered. Further evaluation of testing focusing on these cognitive domains to identify change would be beneficial in future research in to the CSF TT.

Chapter 6 Clinimetric properties and minimally clinically important differences for a battery of gait, balance, and cognitive examinations for the tap test in idiopathic normal pressure hydrocephalus

This chapter has been published in *Neurosurgery*.[96]

6.1 Synopsis

Having established a battery of gait, balance and cognitive measures which can identify change from a CSF TT, the question as to what measures should be applied to identify change from a CSF TT can be answered. The question of what constitutes a level of change which should warrant undergoing VP shunt insertion and what combination of tests should be applied to determine when change has occurred has yet to be answered.

Consistently, research on the CSF TT identifies arbitrary cut off values for the CSF TT by which the authors determined the level of change to warrant VP shunt insertion.[45,55,58] To date, no scientific rationale to support these determinations has been developed. Furthermore, a large number of measures have been identified which can be used to identify change from a CSF TT but the question of how many and what combination of tests should be applied is yet to be determined.

This chapter will build on the previous two chapters by analysing the clinimetric properties of the measures found to be able to identify change from a CSF TT. This will facilitate the calculation of minimally clinically important differences (MCIDs) for these measures. The calculation of these values will allow a scientific approach to determining cut off values to support VP shunt insertion. This

chapter will also use MCIDs to calculate sensitivity and specificity values to identify which tests can best identify or exclude when improvement from a CSF TT has occurred.

6.2 Abstract

Background: Idiopathic normal pressure hydrocephalus (iNPH) is treated by insertion of a ventricular peritoneal (VP) shunt. To help identify who would benefit from a VP shunt, patients undergo a Cerebrospinal fluid (CSF) tap test (TT). Several measures can identify change from a CSF TT, but the magnitude of change and the combination of measures that indicate the improvement from a CSF TT is unclear.

Objective: To develop minimally clinically important differences (MCIDs) for a battery of gait, balance and cognitive measures in relation to improvement from the CSF TT and identify which combination of measures best identifies when improvement has occurred.

Methods: Observational study of iNPH patients undergoing a CSF TT for consideration of a VP shunt. Patients completed the: The Timed Up and Go (TUG), Timed Up and Go cognition (TUG-C), Performance Oriented Mobility Assessment (Tinetti) and Berg Balance Scale (BBS) pre and post a TT. A global rating of change scale assessed patients' perceived improvements in gait and balance post TT.

Results: MCIDs for the CSF TT were (calculated as percentage changes): TUG: 13%, TUG-C: 11% Tinetti: 36% and BBS: 20%. A combination of the TUG-C and Tinetti resulted in sensitivity of 90.28% to identify improvement while the Tinetti and BBS resulted in specificity of 98.58% to exclude improvement from a TT.

Conclusion: These MCIDs provide the first evidence to quantify the significance of post CSF TT symptom changes and provides objective data to guide recommendations for clinical management. Utilising a combination of measures, and these MCIDs as cut off values, results in high sensitivity and specificity for identifying improvement from a CSF TT.

6.3 Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition characterised by a combination of gait ataxia, balance disturbance, cognitive decline and urinary incontinence.[10] As the symptoms are similar in nature to Parkinson's disease or Alzheimer's disease, iNPH is typically diagnosed after failure to respond to treatment for these latter conditions.[6,8,97]

Idiopathic normal pressure hydrocephalus is often treated surgically by the insertion of a ventricular peritoneal (VP) shunt, a neurosurgical procedure which involves using a catheter to divert cerebrospinal fluid (CSF) from the ventricles of the brain to the peritoneal space in the abdomen.[7,12,13] Surgical intervention is limited by the fact that not all patients will benefit from surgery, with improvement rates following surgery reported as low as one-third of cases.[7,19,54] Combined with the potential for adverse events post operatively, efforts to improve the rate of surgical success have resulted in the development of procedures designed to temporarily mimic the effects of surgery.[26,48] One such test, the CSF tap test (TT), aims to drain 30-50mls of CSF from patients and assess for symptom improvement. It has been shown that the CSF TT is sensitive to identification of responders to surgical intervention.[24,26,50,54,97]

Which measures should be administered in relation to identifying symptom improvement from the CSF TT is unclear. Similarly, the extent of improvement in symptoms required to suggest a positive result to a CSF TT is yet to be established.[8,62] Previous authors have suggested improvements of 5% or 10% were required to identify a positive response to a CSF TT.[22,91] However, the use of these cut offs to identify improvement is arbitrary and lacking scientific evaluation.

Recent research has sought to identify measures routinely utilised by clinicians to assess gait, balance, upper limb function and cognition which can identify improvement from a CSF TT.[75,98] It was shown that statistically significant improvements could be identified by the TUG, Performance Oriented Mobility Assessment (Tinetti), Berg Balance Scale (BBS) and 10 metre walk test.[75] The 9-hole peg test was unable to identify significant change from a CSF TT while only the sub scores for executive function

and orientation of the MoCA identified change.[98] The TUG-C was able to identify change from a CSF TT with significant differences present between those who improved (labelled responders) and those who did not improve (labelled non-responders), along with large differences between change scores for responders and non-responders.[98] Similarly, it was also shown that the TUG, Tinetti and BBS could differentiate responders to a CSF TT from non-responders.[75] Patients undergoing a CSF TT were also asked to complete a global rating of change (GRC) scale in relation to improvements in their gait and balance. Responders were able to identify when change had occurred, and where no change was reported this was consistent with non-responder status.[98] This work, while identifying measures which could identify improvement from a CSF TT, along with quantifying patients' ability to identify change from a CSF TT, did not establish scores for these measures which could be considered sufficient to warrant deeming a patient to have improved from a CSF TT.

A minimal clinically important difference (MCID) is a value which can be used to develop the cut off score by which significant change has been identified by patients and clinicians. A MCID is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in patients management".[99] Given that several gait, balance, and cognitive measures have been identified which can identify improvement from a CSF TT, the magnitude of change for these measures, either singularly or in combination, considered as clinically adequate to confirm a positive response to a CSF TT needs to be established. On this basis, this study had two aims: 1. determine MCIDs for gait, balance and cognitive measures previously identified as able to identify change from a CSF TT. 2. Identify which combination of measures has the best ability to identify when improvement has occurred from a CSF TT.

6.4 Methods

Patients were recruited from a tertiary referral neurology and neurosurgical facility between June 2013 to December 2016. All patients who were admitted with iNPH and aged over 55 years to undergo a CSF TT were invited to participate. Diagnosis of iNPH was made by the admitting medical officer and consistent with international guidelines on the diagnosis and treatment of iNPH.[6,19] Patients were required to have an Evans index greater than 0.3 on CT or MRI, and the presence of gait or cognitive or incontinence symptoms consistent iNPH which were not explained by any other condition.

Written consent was sought from patients after provision of an information pamphlet explaining the study. Ethical clearance to conduct this research was approved in April 2013. Exclusion criteria were inability to walk 10m with assistance or inability to provide informed consent. Mobility aids were permitted. On enrolment into the study patients underwent a battery of gait, balance and cognitive examinations before and after undergoing a CSF TT. The following measures were assessed:

- Performance Oriented Mobility Assessment (Tinetti)
- Timed Up and Go (TUG)
- Timed Up and Go Cognition (TUG-C)
- Berg Balance Scale (BBS)

The CSF TT was completed by the admitting medical officer and aimed to drain 30mls of CSF. The above measures were administered by the same physiotherapist pre and post CSF TT. On each occasion, patients were given three opportunities to complete each measure with the best score of the three attempts recorded. Post CSF TT assessment was completed 2-4 hours after the CSF TT with the GRC completed immediately after post CSF TT assessment, prior to patients being informed of CSF TT results. The medical officer completing the CSF TT was blinded to research outcomes.

Patients global rating of change

Patients marked on a GRC scale the level of change they had noticed in relation to their gait and their balance on completion of post CSF TT assessment. This scale has been previously utilised as a patient reported measure of change in iNPH.[81] The scale ranges from -5, labelled completely worse to +5, labelled completely improved. Zero was labelled no improvement. Two GRC scales were completed by patients, responding to the questions "with respect to your walking, how much of a change has occurred" and "with respect to your balance, how much of a change has occurred". Patients were additionally guided to compare to their walking or balance immediately prior to undergoing a CSF TT. Patients indicated with a mark on these scales where they perceived change in symptoms was best described. Input from patient's carers when present, was permitted. Patients at times sought input from their carers, which was permitted, to assist in determining a reflective GRC response.

Statistical analysis

Stata 13 (StataCorp, College Station, Texas) was used for statistical analysis. Sample size calculations for this cohort of patients have been previously reported.[75] A sample size of 74 patients were recruited. Based on a previously reported minimal detectable change (MDC) for the TUG of 3.5 seconds, significance levels of 0.05 and power of 0.8, a sample size of 74 patients was determined necessary. The TUG was used as the basis for this calculation as it represented the largest sample size calculation for all measures. Change scores for each outcome were assessed for normality. The TUG and TUG-C were identified as non-parametric.

Prior to MCID calculation, standard errors of measurement (SEM) and MDCs with 95% confidence were calculated for each measure. The formulas used to calculate SEMs and MDCs were used from previously reported methods.[61,76] For the TUG and TUG-C, interquartile ranges (IQR) were used rather

than standard deviations. Intraclass correlation coefficients (ICC) were calculated using one-way analysis of variance for each measure.

Minimally clinically important differences were calculated by two methods. An anchor based calculation was completed utilising GRC scales completed by patients after post CSF TT assessment consistent with previously published methods.[99] Global Rating of Change scores were categorised into four categories: declined (<0), no improvement (0), moderately improved (0-2) and significantly improved (>2). Mean change scores were calculated for each category for all measures. This established a range for which the MCID for each measure could potentially lie.

A second method utilised receiver operating characteristic (ROC) curves for each measure with GRC scores used as a classifying variable. Anchor based ROC approaches have been explored in detail for MCID calculation.[100] Global rating of change scores were dichotomised into improved/not improved with cut off scores at 0, >1 and >2. Receiver operator characteristic curves were calculated for each level of GRC. Minimally clinically important differences identified by this method were selected by identifying cut off scores which exceeded the MDC for each measure, represented the best sensitivity and specificity, and were within the ranges developed in method one.

The TUG, TUG-C and the gait sub score of the Tinetti (Tinetti Gait) were compared against GRC scores for gait, while the balance sub score of the Tinetti (Tinetti Balance), Tinetti and BBS were compared to GRC scores for balance for both MCID calculation methods. All data were presented as both exact values for the measures and also as percentage change from pre CSF TT scores. These values were calculated independently.

Based on sensitivity and specificity values identified by ROC analysis, pooled sensitivity and specificity values were calculated for measure combinations. Calculations were completed on the following combination of measures:

- TUG and Tinetti

- TUG and BBS
- TUG and TUG-C
- Tinetti and BBS
- TUG-C and Tinetti
- TUG-C and BBS

Pooled calculations used formulas based on the completion of measures in parallel. Calculations were completed for both when one measure exceeds a MCID and where both measures exceed MCID's. Formulas for pooled calculations were used from previously established methods. [101] The highest sensitivity and specificity values for each measure from ROC analysis were used. Sensitivity and specificity values were used from percent change ROC analysis.

6.5 Results

Seventy-seven patients were approached for this study, and 76 were recruited. One patient declined involvement and two patients were later excluded due to a misdiagnosis of iNPH leaving 74 participants enrolled in the study. Sixty-eight patients completed a GRC for their gait and balance. As a result, 68 patients were utilised for this analysis. The TUG-C was included in the CSF TT assessment battery after this study was initiated. Interim analysis of the TUG indicated the addition of the TUG-C would allow adequate effect size for statistical analysis from a smaller sample size then was initially identified. As a result, data is available for 26 patients for the TUG-C.

Demographics

A full demographic description of patients enrolled in this study has been previously reported.[75] The median patient age was 75 (IQR 68,80) and the median duration of symptoms was 9 months (IQR 6,12). 47 patients were male and 27 females. The CSF TT drained a mean CSF volume of 29.54mls (SD 4.31mls) across all patients with a median time to completing post CSF TT assessment of 2 hours (IQR 1.5, 2hrs).

Standard error of measurement and minimal detectable changes

Table 6.1 provides a summary of ICC, SEM, and MDC for each measure where calculations of exact change values and percentage change values have been reported.

Table 6.1 ICC, SEM and MDC calculations for individual assessment tests.

	Timed Up and Go*	Timed Up and Go Cognition*	Tinetti	Tinetti Balance	Tinetti Gait	Berg Balance Scale
Intraclass Coefficient	0.94	0.99	0.93	0.76	0.77	0.88
SD /IQR of hange Score+ (exact / % change)	4.85 sec/ 17.62%	3.58 sec/ 19.36%	2.76 / 41.55%	1.49 / 29.13	1.45 /33.63%	3.82 / 22.72%
Standard Error Measurement (exact / % change)	1.19 sec/ 4.32%	0.39 sec/ 1.94%	1.35 / 10.99%	0.73 / 14.27%	0.54 / 16.13%	1.32 / 7.88%
Minimal Detectable Change (exact / % change)	3.29 sec / 11.97%	0.99 sec / 5.38%	3.74 / 30.46%	2.02 / 39.55%	2.33/ 44.71%	3.65 / 21.84%

*Inter quartile range used for standard error of measurement calculations

+ Inter quartile range reported for Timed Up and Go and Timed Up and Go Cognition, standard deviation all other tests

Anchor based MCID calculation

Table 6.2 summarise MCIDs from anchor based calculations. For GRC in gait 3% of patients reported negative change, 37% reported no change, 28% reported moderate improvement and 32% reported significant improvement. The TUG-C had fewer patients completing this measure with 46% of patients reporting no improvement, 23% moderate improvement and 31% significant improvement. For GRC change in balance, 3% of patients reported negative change, 35% no change, 35% mild improvement and 27% moderate improvement.

MCID ranges calculated for each measure were as follows: TUG -26.67% to 5.91%, TUG-C 0% to 20.52%, and Tinetti Gait 16.67% to 39.40%. For the Tinetti Balance the MCID range was 23.86% to 43.57%, the Tinetti 11.89% to 47.45% and for the BBS 3.33% to 19.81%.

Table 6.2 MCID calculations from anchor based methods for GRC for balance with Tinetti Balance, Tinetti and Berg Balance Scale

	Global Rating of Change of Balance			
Change score	<0	0	0-2	>2
Tinetti Balance				
Change Score/ % Change	3.5 / 43.57	0.42 / 7.87	1.63 / 21.48	2.11/ 23.86
N	2	24	24	18
Tinetti				
Change Score/ % Change	3.5 / 43.57	0.67/ 11.89	2.58 / 31.98	4.17/ 47.45
N	2	24	24	18
Berg Balance Scale				
Change Score/ % Change	4.50 / 15	1.17/ 3.33	3.83 / 16.75	6.22 / 19.81
N	2	24	24	18
	Global Rating of Change of Gait			
Timed Up and Go				
Change Score(sec) / % Change	-4.22 / -26.67	-0.13 / -0.99	1.60 / 3.29	5.91 / 5.91
N	2	25	19	21
Timed Up and Go Cognition				
Change Score(sec) / % Change	0 / 0	1.45 / 0	2.37/ 14.60	5.34 / 20.52
N	0	12	6	8
Tinetti Gait				
Change Score/ % Change	1.50 / 16.67	0.24 / 6.48	0.95 / 14.71	1.81 / 39.40
N	2	25	19	21

N, number

Sec, seconds

ROC curve MCID calculations

Table 6.3 summarises MCIDs by ROC curve analysis with sensitivity, specificity and area under the curves (AUC) for each measure. Cut off values for each measure remained the same for each category of improvement, creating a range of sensitivity and specificity for these cut off values. MCIDs were selected based on sensitivity and specificity values for each measure. These were: 20% for BBS, 40% for Tinetti Balance, 36% for the Tinetti, 43% points for Tinetti Gait, 13% for the TUG and 11% seconds for the TUG-C. Figure 6.1 illustrates the ROC curves for GRC change >1 by measure for exact values.

Figure 6.1 Area under curves for TUG-C, TUG, Tinetti and BBS

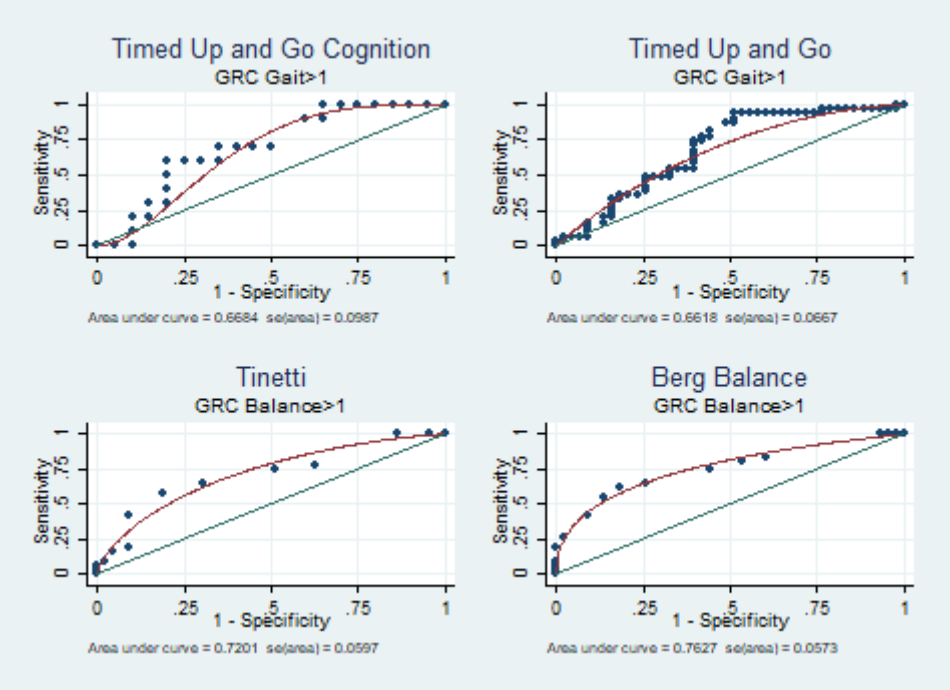


Table 6.3 ROC Curve MCID cut off values for each test with sensitivity and specificity

	Global Rating of Change Balance			**Global Rating of Change Gait**		
	Berg Balance Scale	Tinetti Balance	Tinetti	Tinetti Gait	Timed Up and Go	Timed Up and Go Cognition
MCID (%change)	*20%*	*40%*	*36%*	43%	*13%*	*11%*
MCID (exact value)	*4*	*2*	*4*	*2*	*3.63 sec*	*2.60 sec*
Change>0						
Sensitivity	31.58%	20.00%	50%	17.50%	47.50%	71.43%
Specificity	92.31%	85.19%	81.48%	96.30%	70.37%	75.00%
AUC	0.76	0.68	0.72	0.71	0.66	0.74
Change>1						
Sensitivity	34.48%	19.35%	58.06%	23.33%	46.67%	72.73%
Specificity	88.57%	83.33%	80.46%	97.30%	64.86%	66.67%
AUC	0.78	0.65	0.70	0.69	0.68	0.75
Change>2						
Sensitivity	38.89%	22.22%	61.11%	28.57%	57.14%	75.00%
Specificity	84.78%	83.67%	71.43%	95.65%	67.39%	61.11%
AUC	0.74	0.62	0.71	0.67	0.71	0.75

MCID, minimally clinically important differences

AUC, area under the curve

Table 6.4 Sensitivity and Specificity values for test combinations in parallel.

	Timed Up and Go and Tinetti	Timed Up and Go and Berg Balance Scale	Timed Up and Go and Timed Up and Go Cognition	Tinetti and Berg Balance Scale	Timed Up and Go Cognition and Tinetti	Timed Up and Go Cognition and Berg Balance Scale
Sensitivity						
One test	83.33%	73.81%	89.28%	76.23%	90.28%	84.72%
Two tests	34.92%	22.22%	42.86%	23.77%	45.83%	29.17%
Specificity						
One test	59.94%	64.96%	52.78%	75.21%	52.78%	69.23%
Two tests	91.91%	97.72%	92.59%	98.58%	92.59%	98.08%

Pooled sensitivity and specificity values for measure combinations

Pooled sensitivity and specificity values for response to the CSF TT for one and two measures exceeding MCIDs are summarised in Table 6.4.

6.6 Discussion

This study represents the first calculation of MCIDs for measures used clinically in association with the CSF TT in patients with iNPH. This study provides a methodology to support clear cut off values to identify a clinically relevant change from a CSF TT which would warrant patients being labelled as meaningfully improved following a CSF TT. Outcomes following VP shunt insertion have yet to be addressed by this method, thus the predictive ability of MCID values as they relate to surgical outcomes is not yet known.

Until now, quantification of meaningful change from the CSF TT has been arbitrarily decided. With the development of these MCIDs, patients and clinicians may now have the ability to support decision making related to quantifying improvements from the CSF TT and determining appropriate management for iNPH patients based on the CSF TT outcome. MCID's have been reported as both exact values and percentage changes for the measures utilised. It has been common practice for these measures to have values reported as exact values.[102,103] It is however common place in iNPH literature to determine improvements from a CSF TT based on percentage change.[50,57] As such we have focussed on drawing conclusions from percentage change values.

The use of an anchor based method to calculate MCIDs ensures that these scores reflect patient's perceptions of the significance of change in their symptoms. [99] Based on the definition of a MCID, values were selected from ROC analysis which were above our calculated MDCs. In order to recommend patients have sufficiently improved from a CSF TT, potentially making them candidates for VP shunt insertion, clinicians must be certain that the change which has been measured is real, not the result of measurement error, as well as meaningful for patients. The reliance on the GRC as an anchor to quantify MCIDs may be considered a potential limitation due to known issues related to recall bias.[81] Furthermore, the methods for developing MCIDs have been reported as being controversial due to variation in methodology to develop them.[100] In accounting for this, we used two recognised methods to identify a range with which a true MCID may fall, combined with the use of

ROC analysis to identify specific sensitivity and specificity for selected MCID values to mitigate error. In an attempt to overcome issues of recall bias patients were requested to use a short term anchor by which to measure any change in their symptoms.

Sensitivity and specificity varied significantly across measures for which MCIDs have been calculated. Sensitivity ranged from 31.58% for the BBS to 75% for the TUG-C. Overall, the TUG-C and TUG represented the measures with the highest sensitivity for identifying improvement in patient's symptoms. Specificity values were highest for the BBS and Tinetti Gait at 92.31% and 97.30% respectively. The range of sensitivity and specificity of these measures indicates that none of these measures should be considered in isolation and the use of multiple measures would be beneficial to determine when improvement has occurred from a CSF TT. The TUG-C as a standalone measure appears to have the highest ability to rule in or rule out if change has occurred.

The MCID and MDC values for the TUG and TUG-C were not expected. Given that the TUG-C contains a cognitive item in addition to the standard TUG, it would be presumed this measure would have larger values as the TUG-C takes longer to complete. The high ICC for the TUG-C is likely to be a result of the smaller number of patients who have completed the TUG-C compared to the TUG. The high ICC results in a smaller MDC allowing for the selection of a smaller MCID.

Combining measures to determine improvement from a CSF TT results in improvements in the sensitivity and specificity values to identify improvement. It has been previously shown that statistically significant differences are present for self-reported improvement in gait and balance symptoms in regard to improvements to a CSF TT.[75] On this basis, using self-reported improvement to dichotomise patient outcome for the purpose of calculating sensitivities and specificities was undertaken. Pooling of measures is consistent with clinical practice where routinely multiple measures are utilised to identify improvement from a CSF TT. The values calculated in this population will assist clinicians on the most accurate assessment battery to complete with patients undergoing a CSF TT.

A combination of measures which assess gait and balance results in the highest combination of sensitivity and specificity. Combining the TUG-C and Tinetti or the TUG and Tinetti resulted in high sensitivity values to identify improvement from a CSF TT. Utilisation of the TUG-C and either the Tinetti or BBS results in similar sensitivity and specificity values. This adds further weight to the efficacy of applying the TUG-C given its additional ability to assess cognitive function through dual tasking while completing a gait task. The TUG has been reported consistently as a measure for assessing improvement in iNPH. Our research suggests that the TUG-C may further enhance the utility of the TUG.

Failure to improve on any two measures results in high specificity values between 92% and 99%. This suggests failure to improve by the MCID on any two measures is a strong indicator that a patient has not improved following the CSF TT. It has been reported that the CSF TT has low negative predictive value to exclude patients who will improve from VP shunt insertion.[57] These specificity values could suggest that the measures used to identify improvement from the CSF TT may play a role in explaining this low negative predictive value. The assessment regime used and these reported MCID values may result in improved negative predictive values to exclude patients who will not improve from VP shunt insertion.

6.7 Conclusion

Improvement of 20% for the BBS, 36% for and Tinetti, 40% for the Tinetti Balance, 43% for the Tinetti Gait, 13% for the TUG and 11% for the TUG-C represent MCIDs for iNPH patients undergoing a TT for consideration of a VP shunt. The use of the TUG or TUG-C with the Tinetti or BBS forms an effective assessment regime to accurately identify iNPH patients who have improved because of a CSF TT and should be considered for application by clinicians.

Further research is required to identify the extent to which these MCIDs can identify improvement after VP shunt insertion. Research to determine if a predictive ability exists for any of these measures to identify improvements seen following VP shunt insertion will strengthen the clinical relevance of these scores.

Chapter 7 Are gait changes linked to CSF flow changes in the sagittal sinus?

This chapter has been accepted for publication and is press in *Neuroradiology*

7.1 Synopsis

The CSF TT forms only one component of clinical testing which is used to identify patients with iNPH who would benefit from VP shunt insertion. A key diagnostic component is the presence of ventromegaly on CT or MRI scan with an Evans index greater than 0.3.[8] Given the need for patients to undergo radiological investigation to diagnose iNPH, attempts have been made to identify if any radiological markers on MRI examination may be beneficial in identifying patients would benefit from surgery.

This component of the research was made possible by collaboration with the neuroradiologists at the participating facility. The aim was to identify if any radiological markers on MRI CSF flow studies could identify gait improvements from CSF drainage. Results from MRI CSF flow studies were analysed in conjunction with results of the TUG which was used as part of the CSF TT to facilitate an exploratory analysis to identify links between improvements in gait symptoms and markers of CSF flow on MRI.

Anecdotally, the neuroradiologist at the participating facility has long held a hypothesis related to the venous drainage of the cranium as a potential contributing factor to communicating hydrocephalus. Based on this and previous work which has developed a hypothesis related to a common link between multiple forms of communicating hydrocephalus across the lifespan, this chapter seeks to explore data related to venous drainage within the cranium along with CSF flow markers which have been reported previously as indicative and prognostic of improvement from VP shunt insertion.

7.2 Abstract

Purpose: To identify if specific findings on magnetic resonance imaging (MRI) cerebrospinal fluid (CSF) flow studies can be utilised to identify which patients with idiopathic normal pressure hydrocephalus (iNPH) will have improved gait following a CSF Tap Test (TT).

***Methods*:** Prospective study of patients undergoing a CSF TT for iNPH. Functional gait was assessed using the timed up and go (TUG) test before and after the CSF TT. MRI CSF flow studies accompanied the CSF TT. The minimum clinically important difference for the TUG (3.63 seconds) was used as a cut off value to categorise patients as responders to the CSF TT.

Results: 53 patients underwent CSF TT and MRI CSF flow studies. Significant differences were identified between groups for (non-responder vs responder): superior sagittal sinus flow (47.10% vs 40.41%), sagittal sinus stroke volume (274 vs 176.5 µl), sagittal sinus to arterial stroke volume ratio (0.203 vs 0.164), sagittal sinus area (42.2mm^2 vs 36.2mm^2) and circumference (27.7mm vs 24.95mm). No differences were present for aqueduct stroke volume, arterial stroke volume or aqueduct net flow.

Conclusions: A link between gait improvement resulting from CSF drainage and sagittal sinus measurements indicates that the sagittal sinus may play a role in the manifestation of symptoms in iNPH. This may have implications for the diagnosis of iNPH and potentially inform clinical decision making regarding surgical intervention.

7.3 Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition with a triad of symptoms consisting of gait ataxia, cognitive impairment and urinary incontinence in the context of ventriculomegaly of no identifiable cause.[10] Placement of a ventricular peritoneal (VP) shunt is the gold standard for treatment for iNPH. [5,8,10,54] However treatment success is variable, with a proportion of patients showing no signs of improvement following treatment.[7,12,25] Studies have shown that as low as one third of patients who receive a VP shunt demonstrate any improvement in symptoms.[3,7,54]

Poor rates of treatment response may, in part, be contributed to by the current lack of understanding of the pathophysiology of iNPH and the process by which it manifests. [26,36] It is thought that iNPH is a form of communicating hydrocephalus where cerebrospinal fluid (CSF) absorption through arachnoid granulations is impaired preventing CSF absorption from the subarachnoid space.[1,8] This causes CSF volumes to rise and CSF turnover decreases as a result, but no clear mechanism to explain this has been established.[88] One theory related to the development of communicating hydrocephalus supports the elevation of cortical venous pressure as a result decreased transvenular absorption of CSF from interstitial spaces.[104] It has been suggested that this decreased transvenular absorption alters the pressure gradient between ventricles and the cortex, decreasing CSF absorption and increasing CSF pressure triggering a subsequent increase in cortical venous pressure.[104]

Models of pulse wave encephalopathy have been proposed and suggest that a reduction in venous outflow from the cranium results in excessive accumulation of CSF in the subarachnoid spaces and ventricles contributing to iNPH.[36] Other theories propose that arterial hypertension, vascular disease risk factors and diabetes mellitus, are a possible reason for increased white matter lesions contributing to the pathogenesis of iNPH.[29,105,106] Evidence of protein accumulation within arachnoid granulations reducing CSF flow has also been implicated in this condition.[64] Despite multiple theories the exact mechanisms remain elusive. Research in external and communicating hydrocephalus in children has suggested that elevated venous pressures may contribute to symptom manifestation.[107,108]

Measurements of sagittal sinus pressures have shown an elevation, with the suggestion that these changes may be implicated in the development of hydrocephalus.[108] In paediatric hydrocephalus, obstruction of the sagittal sinus has been shown to result in the development of symptomatic hydrocephalus.[27,107,108] Idiopathic intracranial hypertension has also been demonstrated to be related to raised venous pressures.[107,109]

Definitive causative links to the symptoms of iNPH have not been established to date. The venous drainage of the cranium has been proposed as a potential contributor to the development of dementia in iNPH.[110] Bateman in 2002 identified venous compression as a potential cause of dementia in iNPH. Through comparison of individuals with iNPH to individuals with leukoaraiosis and controls it was identified that the pulsatility of the superior sagittal sinus was 70% higher than controls compared to 39-43% higher for leukoaraiosis. [110] It was concluded that the presence of raised venous pressures across multiple conditions may suggest that a common causative issue may be present across all forms of altered CSF absorption, potentially including iNPH. This could explain the development of dementia symptoms in these conditions. This work did not explore other symptoms associated with iNPH.

To date, minimal investigation of MRI CSF flow has focussed on the role of the venous drainage of the cranium in iNPH, rather focussing on arterial and CSF flow. One study has shown that CSF flow rates through the cerebral aqueduct were 95% predictive for the diagnosis of iNPH.[111] Similarly it has been shown that stroke volumes greater than 42µl are a favourable predictor of shunt response.[46] Recent iNPH guidelines concluded patients with high velocity aqueductal flow on MRI are possibly more likely to improve from shunting.[97] Given evidence of common links between the venous drainage of the cranium and several conditions, along with links shown between changes in the sagittal sinus and the development of dementia in iNPH, it would be warranted to explore if other symptoms, such as gait changes, of iNPH may be linked to the sagittal sinus.

To allow identification of potential candidates for VP shunt insertion various supplemental tests are used.[42,85] One method, the CSF tap test (TT), a form of temporary CSF drainage is designed to mimic a

VP shunt.[11,26] This procedure is relatively simple with minimal risk and is used to determine if the more invasive surgical procedure, VP shunt is warranted. Gait is often the symptom most often seen to change from a CSF TT. The rationale underpinning the test is that transient improvements resulting from the CSF TT should be conferred to VP shunt outcomes.[50]

Given the previous links drawn between the development of dementia in iNPH and the sagittal sinus the aim of this study was to determine if differences in measurements of CSF and vascular flow within the cranium on MRI were associated with improvements in gait following a CSF TT.

7.4 Methods

A prospective observational study was conducted in a tertiary referral neurological and neurosurgical facility in Australia from April 2013 to December 2017.

Recruitment

Patients admitted to the facility with a diagnosis of iNPH consistent with international guidelines, for a CSF TT procedure, and who underwent a MRI at the same facility, were invited to participate.[6,8] Patients were provided with written information detailing study involvement and written consent was sought from the patient or next of kin.

To be considered for inclusion patients were required to be: aged over 55 years, able to walk 6m with or without a mobility aid or assistance, undergoing an MRI at the participating facility and a CSF TT for consideration of a VP shunt. Patients were excluded if they were ineligible for an MRI or had an MRI completed at an external facility due to inability to collate MRI data from external facilities.

MRI CSF flow studies

All patients were imaged on a 1.5 T superconducting magnet (Avanto; Seimens, Erlangen Germany). The patients were scanned with standard T1 sagittal, T2 and FLAIR axial images. The MR flow quantification sequence was acquired as a phase contrast study with retrospective cardiac gating. The TR was 26.5 m/sec, TE 6.9 m/sec, flip angle 15 degrees, slice thickness 5 mm, matrix 192 x 512, FOV 150 and a single excitation. The velocity encoding values were 20 cm/sec for the aqueduct flow, 40 cm/sec for the venous flow and 75 cm/sec for the arterial flow. The plane was selected to pass through the mid portion of the aqueduct for the aqueduct acquisition, to pass from the sagittal sinus 2cm above the torcular and through the mid part of the straight sinus for the venous acquisition and along the skull base to pass through the carotid arteries and the basilar artery for the arterial acquisition. The planar imaging, as well as the flow quantification raw data, was archived on the hospital electronic radiology system.

Readings were taken for the following parameters on MRI for flow: aqueduct stroke volume, aqueduct net flow, arterial stroke volume and flow, straight sinus flow, sagittal sinus flow, sagittal sinus stroke volume, sagittal sinus to arterial stroke volume ratio, compliance ratio and sagittal sinus area and sagittal sinus circumference. Using the flow quantification data, regions of interest were placed around the aqueduct, carotid arteries, basilar artery, sagittal and straight sinuses in each patient. Care was taken to exclude aliasing by retrospectively manipulating the base lines of each resultant graph. Background subtraction was utilized to minimise the effect of eddy currents.

The net flow in the aqueduct, arteries and sinuses was derived by the multiplication of the average flow velocity across the region of interest in each for the entire cardiac cycle by the cross-sectional area of the region of interest. The stroke volumes at each site represent the volume increase in fluid/ blood which occurs at each site in systole over and above the mean flow i.e. as the flow pulsates the

increase in flow in systole equals the decrease in diastole and the stroke volume represents this change in flow volume. A ratio of the aqueduct stroke volume to the arterial stroke volume comprised the compliance ratio. A similar ratio from the sagittal sinus stroke volume to arterial stroke volume was performed.

The cross-sectional area of the sagittal sinus was measured from the T2 images from a slice selected to be 3 cm above the torcular with both the area and circumference of the sinus measured using the scanners measurement tool. Figure 1 provides a representation of where these measures were taken.

CSF Tap test

Patients underwent a CSF TT draining 30mls of CSF and were assessed using a battery of gait, balance and cognitive assessments before and after the CSF TT. Post CSF TT assessments were conducted within 3 hours of the procedure. Patients were asked to complete a timed up and go test (TUG) as part of this assessment battery. The TUG has been shown to be an effective test to identify change from a CSF TT. [75] The TUG requires the patient to rise from a chair, walk 3 metres and return to the chair whilst being timed. This was conducted by the same Physiotherapist pre and post CSF TT. Patients were given three opportunities to complete the TUG on each occasion with the best time recorded.

Assessor blinding

The Neuroradiologist reporting on MRI studies was blinded to all clinical assessments related to the CSF TT and the Physiotherapist completing the clinical assessments was blinded to MRI results.

Ethical approval

This study was approved by the Hunter New England Human Research Ethics Committee, reference; 13/06/19/4.02 in April 2013.

Determination of response status

Previous research has established the minimally clinically important difference (MCID) for the TUG in iNPH to be 3.63 seconds.[96] For this study patients with a TUG change score equal to or greater than the MCID (≥3.63 seconds) were considered to have improved and were classified as responders. Patients with a TUG change score less than the MCID were classified as non-responders.

Statistical analysis

Patients were dichotomised into responders and non-responders based on TUG results for the purpose of analysis. Chi squared tests were completed on patient demographic data. Skewness kurtosis tests were completed to assess normality. Based on this, Mann Whitney U tests were used to assess between group differences.

Response status was used to classify outcomes for ROC curve analysis. ROC curves were developed for all values. Stata 13 (Stata Corp Tx) was used for statistical analysis with significance levels set at 0.05.

7.5 Results

Nineteen of the 53 patients enrolled in the study were deemed to be responders to the CSF TT, 34 patients were non-responders. The median time to clinical assessment post CSF TT was 2 hours and a mean of 30mls of CSF drained with no between group differences in these parameters.

Demographics

A summary of patient characteristics is presented in Table 1. No significant differences were present on any variable except gender.

Table 7.1 Patient demographics by response

	Study Population (n=53)	CSF TT Non-Responders (N=34)	CSF TT Responders (N=19)	P value
Age*	72 (11.80)	72 (8.28)	71 (16.90)	P=0.86
Gender (M/F)	33/20	23/12	10/8	**P=0.03**
Symptom duration* (Months)	10.5 (6,12)	10.5 (6,18)	10 (6,12)	P=0.61
Time to post CSF TT assessment*	2 (1.5, 2.5)	2 (1.5, 2.5)	2 (1.5, 3)	P=0.09
Time from MRI to CSF TT* (days)	38 (1,107)	35 (1,87)	74 (1,203)	P=0.36
CSF Volume drained(mls)	30 (4.9)	29.73 (4.59)	29.06 (5.54)	P=0.66
Percent of triad present (Gait/Cognition/ Incontinence)	92/83/45	89/80/46	100/89/44	P=0.80
Number of triad symptoms present 3/2/1 (count)	23/19/11	14/12/9	9/7/2	P=0.46

*Results median (IQR), all other results mean (SD)

MRI findings by response to the CSF TT

Between group differences for MRI measures based on response status to the CSF TT are summarised in Table 2. Significant differences were found between responders and non-responders for superior sagittal sinus flow (SSS) sagittal sinus stroke volume, sagittal sinus to arterial stroke volume ratio, sagittal sinus area and sagittal sinus circumference. No significant differences were found for aqueduct stroke volume, aqueduct net flow, arterial stroke volume, compliance ratio, arterial inflow or straight sinus flow.

Table 7.2 MRI values by CSF TT response

MRI Value [median (IQR)]	CSF TT Non-Responders (N=34)	CSF TT Responders (N=19)	P Value for between group difference
Aqueduct stroke volume (µl)	140 (96,200)	145 (60,200)	P=0.80
Aqueduct net flow (ml/sec)	0.003 (-0.01,0.02)	0.010 (-0.009, 0.05)	P=0.18
Arterial stroke volume (µl)	1342 (943, 1666)	1183 (943, 1420)	P=0.31
Arterial Flow(ml/sec)	8.65 (7.37, 9.62)	9.38 (8.43,9.97)	P=0.07
Straight Sinus flow (ml/sec)	1.26 (1.05, 1.57)	1.23 (1.16, 1.44)	P=0.93
Sagittal Sinus flow (ml/sec)	4.16 (3.29, 4.69)	3.62 (3.32, 4.23)	P=0.32
Superior Sagittal Sinus (SSS) flow (%)	**47.10 (40.65,53.62)**	**40.41 (37.08,47.20)**	**P=0.04**
Sagittal Sinus stroke volume (µl)	**274 (178,412)**	**176.5(153,270)**	**P=0.02**
Sagittal Sinus to arterial stroke volume ratio	**0.203 (0.153, 0.283)**	**0.164 (0.125,0.183)**	**P=0.02**
Sagittal Sinus area (mm^2)	**42.2 (39.5,49.2)**	**36.2 (31.4, 41.8)**	**P<0.01**
Sagittal Sinus circumference (mm)	**27.7 (25.24,30.4)**	**24.95 (23.1,25.8)**	**P<0.01**

All results median(IQR). **Bold text represents statistically significant result**

ROC Curve Analysis and Cut off Values

Table 7.3 summarises AUC, sensitivity, specificity along with positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for CSF TT results. Figure 7.1 illustrates the ROC curve for Sagittal Sinus area and 7.2 for Sagittal Sinus Circumference.

Table 7.3 Cut off values and Clinimetric values for MRI measurements

Measure	Cut off Value	Sensitivity	Specificity	AUC	LR+	LR-
Superior Sagittal Sinus Flow (%)	38.6	82.86%	44.44%	0.67	1.49	0.39
Sagittal Sinus Stroke Volume(µl)	173	80%	50%	0.71	1.6	0.40
Sagittal Sinus to arterial stroke volume ratio	0.164	74.29%	50%	0.69	1.49	0.51
Sagittal sinus area(mm^2)	37.2	91.43%	55.56%	0.75	2.06	0.15
Sagittal sinus circumference(mm)	24.81	82.86%	44.44%	0.75	1.49	0.39

Figure 7.1 Sagittal sinus area ROC Curve

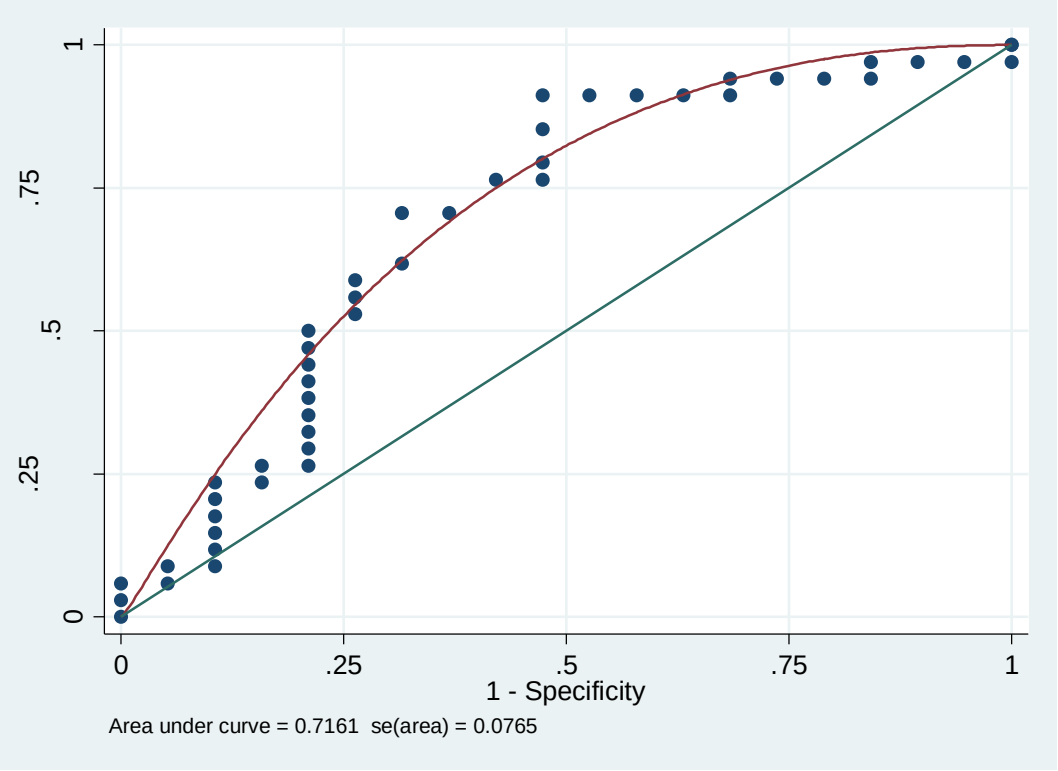
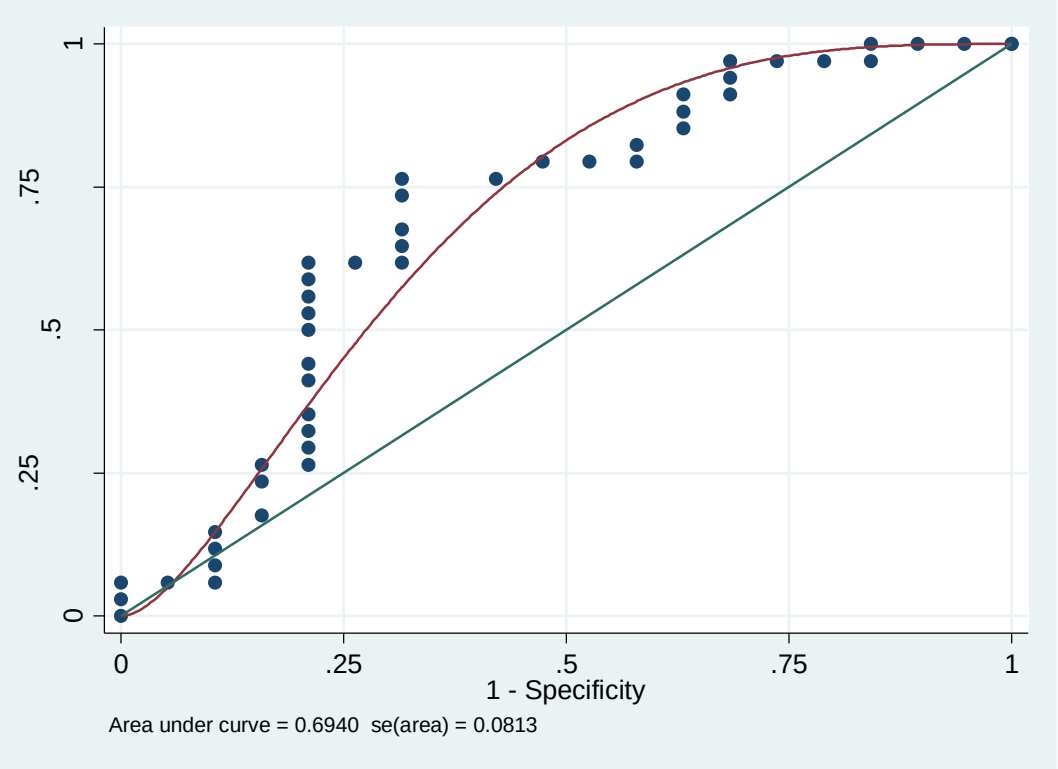


Figure 7.2 Sagittal sinus circumference ROC curve



7.6 Discussion

This study has identified consistent findings related to improvement in gait from CSF drainage via a CSF TT and measurements of the sagittal sinus. No research to date has identified any findings related to the sagittal sinus, iNPH and a link to change in gait symptoms. Previously, research implicating the sagittal sinus' involvement in iNPH has drawn links to dementia symptoms of iNPH.[110] This research now shows evidence that changes in the sagittal sinus are implicated in the development of 2 of 3 of the triad of symptoms in iNPH. The consistency of our findings adds additional evidence to the hypothesis that the sagittal sinus has some implication in iNPH physiology and its measurement may have an important clinical and prognostic role.

Previous research has focussed on the role of the cerebral aqueduct in terms of flow as a diagnostic marker and potential prognostic tool in identifying iNPH.[111-113] We did not find any difference in aqueduct flow between responders or non-responders for a CSF TT. This appears to be consistent with recent research questioning the use of aqueduct net flow to identify shunt responsive iNPH.[112]

This exploratory analysis highlights that patients with iNPH who respond to CSF drainage have lower values on almost every measurement taken for the venous system and higher for every value of the arterial system. While not all of these measurements were statistically significant, the consistency of these findings could suggest that pathology of the vasculature of the cranium may contribute to iNPH. Previous research has shown links between changes in vascular dynamics, specifically hypertension and iNPH.[105] However the findings of this study provide a more detailed link between vascular dynamics and improvements in gait symptoms suggesting that there is compression of the sinuses as indicated by sagittal sinus area and circumference changes, and maybe an increase in the trans mural pressure accompanying this.

When considering superior sagittal sinus flow it appears the sinuses are much more non-compliant in those who see gait improvement from a CSF TT. The higher values recorded for those who do not see gait improvement could suggest that greater flow through the sagittal sinus negatively impacts the effectiveness of CSF drainage techniques. Similarly, it may suggest patients who demonstrate clinical

improvement in gait may have cranial vascular changes which are less severe or yet to develop to the same degree as those who do not respond.

ROC curve analysis demonstrates that sagittal sinus area, flow and circumference can successfully identify improvements in gait resulting from CSF drainage. The AUC for sagittal sinus area and sagittal sinus circumference combined with high sensitivity and specificity values at the selected cut off values indicates these measures have the ability to identify whether patients will experience gait improvements following CSF drainage. The AUC of other MRI measures suggest these tests are not useful in determining gait improvements from CSF drainage.

Sagittal sinus area, flow or circumference are not currently used measures to identify iNPH. Recent research has concluded that the sagittal sinus outflow resistance must be significant in the pathophysiology of other forms of hydrocephalus. [108] This research suggests these findings are also present for iNPH. In the presence of evidence now implicating the sagittal sinus in relation to dementia and gait symptoms in iNPH this would add weight to support the hypothesis that the sagittal sinus changes may be related to iNPH causation and warrants further investigation.

The findings in relation to sagittal sinus measures and patients who respond to CSF drainage is logical in relation to the flow of CSF. Any restriction related to the flow of CSF in the venous system will result in a flow on effect throughout the CSF circulation within the cranial vault. These changes may not be large in scale but over a time could result in significant changes in the flow of CSF and result in adaptive changes to a rising volume of CSF.

The possible effect of confounders in this study cannot be excluded due to the research design and the large number of measures analysed. However, despite these limitations, the findings are consistent across the CSF TT and confirmation with further research is warranted. Additional research is required to determine if the results of this research exist after VP shunt insertion.

7.7 Conclusion

The findings of this study provide additional evidence indicating changes in CSF flow through the sagittal sinus and the size of the sinus are altered in iNPH and implicated in the development of symptoms of iNPH. Furthermore, the extent to which changes occur in the sagittal sinus may provide the opportunity to differentiate patients who will experience gait improvements from CSF drainage as opposed to those who will not. Whether these changes in the sagittal sinus are as a result of, or causative of iNPH, is not clear from these findings.

Further research to confirm these findings post VP shunt are warranted in addition to further work regarding the role of the sagittal sinus in iNPH. Findings suggest that changes in the sagittal sinus may be associated with the development of iNPH and may be used to assist diagnosis and predict response to treatment of iNPH patients into the future.

Chapter 8 Discussion

8.1 What we knew about the TT

Since its description in the early 1980's, the CSF TT has become a routine clinical test by which identification of iNPH patients who would benefit from VP shunt insertion could be made. It's simple, easy application has seen its adoption clinically worldwide and it has been given a strong emphasis as a predictor of outcome post VP shunt insertion in multiple iNPH guidelines.[6,8,97] It is well established that a positive response to a CSF TT has a strong positive predictive value for response to VP shunt insertion.[57] However, it has also been determined that failure to improve from a CSF TT does not accurately exclude patients from improving following VP shunt insertion. Low negative predictive values have consistently been reported for the CSF TT and patients may have been excluded from surgery based on the incorrect assumption that failure to improve from a CSF TT would exclude improvement from VP shunt insertion.[57,114]

A large variety of measures have been reported in relation to assessing response from a CSF TT. Many different standardised measures for assessing gait, balance, cognition and upper limb function are utilised clinically and as research outcomes to assess response to a CSF TT. To date no work has evaluated the reliability of any test to identify change or identify cut off values for which change should be considered as responding to a CSF TT. No previously published research has established clinometric properties such as MDC's or SEM for these tests in an iNPH population. Multiple studies report cut off values of 5% or 10% as values by which positive response was measured.[50,57] These arbitrary cut off values may not accurately reflect true values by which response should be determined.

8.2 What this research has added regarding the CSF TT

This research demonstrates evidence to support the use of a battery of gait, balance, and cognitive measures which can identify change from a CSF TT. A range of measures have been reported for use in relation to the CSF TT and ELD, and this series of studies has demonstrated a group of simple, regularly utilised outcome measures which can identify change from a CSF TT. However, this list of measures is not exhaustive of all measures which may be beneficial in recognising change following a CSF TT.

We determined that the TUG, Tinetti, BBS and TUG-C can accurately identify change from a CSF TT. Delineation between responders and non-responders is possible based on the magnitude of change seen on these tests. Furthermore, patients undergoing a CSF TT can themselves identify when change has occurred adding to the clinical relevance of the change experienced by the patient. Based on the difference in the magnitude of change between the TUG and the TUG-C it appears that the cognitive change does have an impact on the improvement seen on the TUG-C. If the magnitude of change seen was consistent across the TUG and TUG-C then this would not be the case. This combined with MCID's of 13% for the TUG, 11% for the TUG-C, 36% for the Tinetti and 20% for the BBS, can allow clinicians to quantify when change measured by these measures from the CSF TT represent clinically significant changes from CSF drainage. High sensitivity and specificity values related to combinations of these tests provides additional evidence for clinicians to utilise when determining if meaningful change has occurred.

Furthermore, through the development of MCID's for each of these tests, we have established a cut off value by which clinical significance for patients and clinicians determines the importance of change seen from the CSF TT.

8.3 What we knew about the pathophysiology of iNPH

A growing body of evidence has supported the role of altered vascular dynamics as a potential contributing factor to the manifestation of iNPH.[29,40,41,115] It has been identified from the 1990's that hypertension and diabetes mellitus may have a contributing role in iNPH.[40,106] More recently the role of hypertension and its prevalence in iNPH populations has been highlighted.[29,30]

A greater understanding of the role by which vascular disease may be involved in the manifestation of iNPH is beginning to emerge. In the context of the growing links demonstrating an association between vascular disease and iNPH the label idiopathic may soon not be required.

8.4 What this research has added to the knowledge of iNPH pathophysiology

This research provides evidence to further support a vascular component in the manifestation of iNPH. Differences present in measures of the sagittal sinus in patients whose gait symptoms improve following CSF drainage compared to those who did not improve suggest that the venous drainage of the cranium is implicated in the manifestation of iNPH.

Physiologically, a reduction in flow out of the cranium would result in excessive CSF accumulation within the subarachnoid space and ventricles. The differences between sagittal sinus circumference, area and flow between responders and non-responders suggests that the sinus may reach a point where its dilation is non-reversible causing permanent damage and preventing symptoms from improving as a result of VP shunt insertion.

To date, research has focussed on the role of arterial disease and arterial flow within the cranium and its effects on CSF flow and absorption. This seems logical given the role arterial pulse waves play in

CSF pulsatility through the cranium. What is not clear is whether these findings related to the sagittal sinus are causative or a result of iNPH. Further research will be required to establish this association.

8.5 What are the clinical implications of this research?

Clinicians have traditionally used a range of tools to assess symptom change in iNPH. We have identified several tests which are the most useful in identifying change from a CSF TT in iNPH. This research has also established what measures cannot identify change from a CSF TT. More specifically, the MoCA and 9 HPT were unable to identify meaningful change from a CSF TT in this population. The 10MWT, was able to identify statistically significant change, however the effect size was of a magnitude which could be attributed to measurement error. It should be noted that the 10MWT is consistently reported for its efficacy in assessment of iNPH patients in relation to the CSF TT and post-surgical outcomes, making these findings potentially contentious in the context of the body of work utilising the 10MWT.

Given that previous work by other authors in iNPH related to the use of the 9 hole peg test in external lumbar drainage did not show a significant between group difference it was determined that this too was the case for the 9 hole peg test in this population. [11]Other upper limb tests which require a higher level of cognitive processing to perform have been evaluated and been shown to be effective at identifying change in iNPH.[45] As such the conclusion was reached that the 9 hole peg test is not effective and other tests utilizing the upper limb would be best evaluated in the future.

This research provides evidence for clinicians regarding meaningful change for patients in relation to a battery of tests for the CSF TT.[96] MCIDs for the TUG, TUG-C, Tinetti and BBS can guide clinicians on what the level of change identified from a CSF TT means for them clinically and the significance of this change. Clinicians wishing to interpret meaning from results from the CSF TT have evidence by which they can evaluate the response of their patients.

Identification of differences in measurements of the sagittal sinus in patients who respond to a CSF TT which have been identified by this research may have future clinical applications. The strong sensitivity values attributed to cut off values for sagittal sinus circumference and area may provide a new clinical tool by which identification of patients who respond to CSF drainage is possible. Furthermore, the non-invasive nature of MRI CSF flow studies may allow the use of measurements of the sagittal sinus to exclude patients from undergoing a CSF TT avoiding the risks associated with this invasive procedure.

8.6 Limitations of this research

There are limitations associated with the methodological design of this research. This thesis has consistently identified that arbitrary values have been used to determine response status across iNPH literature and often only expert opinion is utilised to determine when a patient has responded to a CSF TT.

In the absence of any scientifically determined ability by which to determine when change has occurred from a CSF TT the methodology of this thesis has too needed to rely on expert opinion. Specialist neurologist of neurosurgeon opinion was utilised to determine response vs non response status in chapter 4 and 5. This subjective selection criteria could not be completely consistent between all neurologists and neurosurgeons. This leads to potential impacts on bias related to determination, impacting on the determination of response status.

Additionally, due to the observational nature of this study the results of gait, mobility and cognitive testing were available to the AMO when determining response status of the patient in chapter 4 and 5. While response status was not determined on CSF TT result alone by the neurologist or neurosurgeon making the determination, the availability of these test results has the potential to confound the findings of this research. In the absence of any scientifically validated method by which

determination of response to CSF TT could be measured there was limited ability to overcome this potential confounding impact.

8.7 Direction of future research

Further investigation is required to determine if the findings of this research will impact on clinical practice and assist to improve surgical outcomes for patients. It is feasible to presume that improved accuracy of patients who improve from a CSF TT would improve the outcome of patients who undergo VP shunt insertion. This however has not yet been evaluated to ascertain if this presumption holds true. What magnitude of measured improvement from a CSF TT predicts or correlates to improvement after VP shunt insertion requires further evaluation. The role these MCID's may play in any correlation or predictive model requires evaluation before they can be used to guide clinical decision making related to progression to VP shunt insertion. Additional future analysis of data collated as a part of this thesis will be used to address questions related to the value of these MCID values and post-surgical outcomes.

This research forms the foundation for further detailed assessment of the impact of the cranial vascular system in the development of iNPH. Evidence linking the sagittal sinus area and circumference to changes in gait as a result of CSF drainage would suggest the potential for a causative relationship to exist between vascular changes and iNPH. Physiologically, changes in the sagittal sinus would result in alterations in CSF absorption through arachnoid granules, something which is established as impaired in iNPH. No clear mechanism has been identified to explain changes in CSF absorption through arachnoid granulations. It may well be because changes in absorption are not caused by changes in the granules themselves but changes in pressure gradients between the sub arachnoid space and sagittal sinuses as a result in changes in the size of these sinuses. Similarly, decreased absorption through arachnoid granulations of CSF results in overall increases in CSF volume causing communicating hydrocephalus. The chronic nature of these changes results in compensatory

compression of the brain parenchyma resulting in the normal CSF opening pressures on invasive monitoring.

Determining if these changes in the sagittal sinus are causative or a result of iNPH may lead to earlier detection and treatment of iNPH and may also have further implications in treatment and diagnosis of other neurodegenerative diseases with similar symptoms and presentations to iNPH. This would have implications for the burden of disease iNPH represents to the community and result in improved surgical outcomes by better and earlier identification of patients with iNPH.

8.8 Conclusion

This thesis has presented a number of outcome measures which can be utilised to identify and measure change from a CSF TT in iNPH. The use of the TUG, TUG-C, Tinetti and BBS are supported by the studies presented in this thesis. What constitutes a MCID by which improvement from a CSF TT has occurred further supports clinicians in the application of these measures when assessing for change from a CSF TT. Utilising the TUG MCID score from a CSF TT to dichotomise MRI CSF flow results in the same population suggests that a link between measurements of the sagittal sinus and improvements in gait as a result of CSF drainage may be present.

Further work from these findings should seek to evaluate the prognostic value of these MCID values to determine outcome post VP shunt insertion. Further research into the significance of these findings related to changes in the sagittal sinus and its ability to identify gait improvement from CSF drainage should occur to substantiate the clinical significance of these findings.

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Appendices

TITLE AND CITATION	Idiopathic Normal Pressure Hydrocephalus: What is the Physiotherapists role in Management?

AUTHOR POSITION	AUTHOR	SPECIFICS OF CONTRIBUTION TO RESEARCH REPORTED AND WRITING OF THE FINAL PAPER	% CONTRIBUTION TO PAPER	SIGNATURE
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TITLE AND CITATION	Gait and Balance measures can identify change from a Cerebrospinal fluid tap test in Idiopathic Normal Pressure Hydrocephalus

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Narrative Review

Idiopathic normal pressure hydrocephalus, what is the physiotherapist's role in assessment for surgery?

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Background: Idiopathic normal pressure hydrocephalus (iNPH) is a condition resulting in a symptom triad of gait ataxia, cognitive impairment, and urinary incontinence. Idiopathic normal pressure hydrocephalus presents a diagnostic and management dilemma such that management involves the placement of a ventricular peritoneal (VP) shunt to which not all patients will respond. Cerebrospinal fluid (CSF) drainage tests such as the lumbar puncture tap test (TT) provide a prognostic indication of response to shunting. However, determination of what constitutes a positive response to shunting is not clearly defined. While gait improvement following TT has been identified as a possible prognostic indicator, the efficacy of such measures in this clinical population has not been tested.
Objectives: To explore the literature related to gait and balance changes associated with iNPH and to identify the possible role physiotherapists might play in the diagnosis of patients with iNPH.
Major findings: Gait changes in iNPH patients have been well documented and improvement following TT has been identified as a strong prognostic indicator of improvement following VP shunt insertion. No research has been identified looking directly at balance changes in patients with iNPH following TT or VP shunt insertion and the efficacy of objective gait assessments in this patient population has not been evaluated. No studies have determined the predictability of improvement after shunting based on measured gait improvements following TT.
Conclusions: Physiotherapists are expertly placed to be involved in the assessment of symptoms of iNPH. However, further research is required to validate balance and gait assessment in this patient group to determine if prediction of shunt outcome is possible using gait assessment after the TT.

Keywords: Idiopathic normal pressure hydrocephalus, Lumbar puncture tap test, Physiotherapy, Physical therapy

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition with a triad of symptoms including gait ataxia, incontinence, and impaired cognition.[1,2] Idiopathic normal pressure hydrocephalus is typically diagnosed in the presence of this classical triad of symptoms together with ventriculomegaly on imaging, and elevated within normal cerebrospinal fluid (CSF) opening pressure on lumbar puncture.[3] Idiopathic normal pressure hydrocephalus was first described in 1965 by Hakim and Adams in a series of case presentations where symptoms improved following removal of CSF.[4] Debate about management and diagnosis of iNPH continues and it is postulated to be a major reversible cause of cognitive and mobility decline in the geriatric population.[5] Cognitive changes in iNPH are suggestive of subcortical dementia due to its presenting symptoms and iNPH is considered a treatable form of dementia.[2,6] Often iNPH manifests in the presence of a diagnosis of Alzheimer's disease or other form of dementia and links have been drawn between the pathophysiology of the two.[7,8]

Two forms of normal pressure hydrocephalus have been described: idiopathic and secondary. Idiopathic normal pressure hydrocephalus occurs in the geriatric population in the absence of any pre-existing factors or insults to explain the change in CSF dynamics. Secondary normal pressure hydrocephalus occurs as a result of previous neurological insult such as trauma, stroke, or congenital abnormality and may occur at a younger age.[2] This delineation of diagnosis has only recently been articulated in research, contributing to the lack of consensus on management of iNPH.[9] Agreement on the prevalence of iNPH has yet to be established, but has been calculated at between 15.2/

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100 000/year and 21.9/100 000/year. An incidence of between 3.74/100 000/year and 5.5/100 0000/year has also been calculated.[10,11] Idiopathic normal pressure hydrocephalus is estimated to affect between 9 and 14% of patients admitted into care facilities.[12]

Current management options focus on the removal of excessive CSF via the insertion of a ventricular peritoneal (VP) shunt. Diagnostic criteria for iNPH and criteria for predicted responsiveness to shunt placement are not always consistent.[2,13,14] Consensus is lacking in relation to a set of definitive diagnostic criteria, although attempts have been made to develop these.[6] Diagnosis is achieved through a combination of clinical and radiological signs.[6] A further dilemma for clinicians is that a diagnosis does not always result in a positive response to treatment.[6] To overcome this, supplementary tests involving the drainage of CSF have been developed to identify potential responsiveness to shunting.[15] However, determination of who might benefit from the removal of CSF via the insertion of a VP shunt remains dubious.[16,17] Several supplementary tests have been used, including drainage techniques such as the lumbar puncture tap test (TT) and external lumbar drainage (ELD), as well as radiological investigation including MRI flow studies and radionuclide cisternography.[2,13,18] The TT, the most commonly used procedure, aims to identify patients most likely to respond to shunt insertion by removal of approximately 30–80 ml of CSF, and assessing symptom change.[13,18,19]

Controversy remains regarding which measured parameters might determine a patient's possible response to the TT.[15] Physiotherapists are regularly called upon to assess gait and balance before and after patients undergo TT to determine improvement.[1] However, little evidence exists around the accuracy of such assessments and no validation of standard physiotherapy instruments such as the timed up and go (TUG), 10 m walk test, or Berg balance assessment has been performed in this patient group.[19]

Diagnosis and Management of iNPH

Since its description in 1965, consensus on accurate diagnostic criteria for iNPH has been lacking. Previously, emphasis was placed on shunt responsiveness as a diagnostic criterion, with true iNPH said to be that which responded to shunt placement.[2,6,13,20] However current guidelines do not make reference to shunt responsiveness in diagnostic criteria. Rather, it is suggested that iNPH should be considered as a diagnosis in any patient with an insidious onset of the symptom triad.[6,13,15] Typically, patients who have had symptoms less than 18–24 months have the greatest potential to respond to shunt placement.[17]

Accurate diagnosis of iNPH requires the coexistence of signs from a patient's clinical history, together with physical and radiological examination. The presence of ventriculomegaly on CT or MRI scan with an Evans index >0.3 is considered a key factor in diagnosis, but not in isolation. The Evans index is a measure of the ratio of maximum width of the frontal horns of the lateral ventricles to the maximum width of the inner table of the cranium.[13] Patients are required to have a CSF opening pressure in the range of 5–18 mmHg on lumbar puncture.[6,13] While the current guidelines, given in Table 1, differ

Table 1 Diagnostic criteria based on published guidelines (abridged)

Marmarou *et al.*[2]	Mori *et al.*[13]
Probable iNPH	Probable iNPH
• Onset>40 years of age	• Meets all requirements for possible iNPH
• Duration of at least 3–6 months	• CSF pressures of 200 mm H_2O or less
• No evidence of any cranial trauma or pathology or secondary NPH	• Imaging showing narrowing of sulci and subarachnoid spaces over midline surface with gait disturbance present
• No other diagnosis to explain the symptoms and their progression	Improvement of symptoms after CSF drainage
• Radiological imaging showing:	Possible iNPH
- Evans index>0.3	• Onset>60 years
- Enlargement of temporal horns of later ventricles	• Evans index>0.3
- Altered brain water content on CT or MRI not attributable to other diagnoses	• Symptoms not explained by other diagnosis
• Gait ataxia with specific signs	• No medical history capable of explaining ventricular dilation
• Cognitive changes with specific signs	Supportive features of possible iNPH
• Incontinence with specific signs	• Gait ataxia most prominent feature followed by cognitive impairment and urinary incontinence
Possible iNPH	• Sylvain fissures and basal cistern enlarged on imaging
• Subacute mode of onset	• Co-existence of Parkinson's or Alzheimer's disease in mild forms
• Begin at any age	
• Non progressive in nature	
• Radiological signs that may be due to atrophy	
• Gait ataxia, incontinence, or dementia alone	
• CSF opening pressure outside expected range	

iNPH: idiopathic normal pressure hydrocephalus; CSF: cerebrospinal fluid.

regarding such factors as the minimum age and duration of symptoms, correlation exists between all other criteria. Common criteria are listed below.

A. Onset:
   - insidious;
   - origin after 40 years of age;
   - minimum duration of 3–6 months;
   - no evidence of an incident event such as head trauma, intracranial haemorrhage, meningitis, or similar conditions;
   - no medical or psychiatric condition sufficient to explain the presenting symptoms.

B. Clinical signs considered mandatory for diagnosis:
   - gait abnormality;
   - decreased motor speed.

C. Cognition changes considered mandatory for diagnosis:
   - decreased attention or recall;
   - impaired executive functioning or multi step functioning.

D. Urological signs unable to be explained by other underlying condition of which two must be present:
   - increased urinary urgency characterized by pressing need to void;
   - increased urinary frequency (>6 voids in a 12 hour period);
   - nocturia (>2 voids overnight).

Pathophysiology of iNPH

Currently there is no viable model related to the development and pathophysiology of iNPH.[13] The manifestation of iNPH has been postulated to be caused by CSF circulatory failure and impaired clearance of CSF through arachnoid granulations.[7] Tenuous links have also been postulated between the pathophysiology of iNPH and Alzheimer's disease, based on the connection between altered CSF dynamics and the presence of amyloid beta in interstitial brain fluid.[8] Currently, neither of these theories have compelling evidential support.

Links have been demonstrated between vascular pathology and iNPH.[21] Associations between iNPH and arterial hypertension along with diabetes mellitus have been demonstrated. It has been postulated that arterial hypertension may result in increased white matter lesions contributing to the pathogenesis of iNPH. This hypothesis however, remains unproven.[21] It is possible that common links exist between the pathogenesis of Alzheimer's disease, iNPH, and vascular disease. However, cause and effect of any common pathogenesis remains unproven.[21]

Normal CSF production has been calculated at a rate of 0.4 ml/minute, the average human adult has a CSF volume of around 150–160 ml with a turnover of roughly four times the volume/day. Cerebrospinal fluid volume and turnover have been shown to be impaired in iNPH populations, with CSF volumes rising to around 200 ml and turnover decreasing to less than 1.5 times the volume per day. This decrease in clearance has been postulated to be a result of increased resistance to the clearance of CSF.[8]

The pathogenesis of the triad of symptoms seen in iNPH has not been well established. It was initially theorized that ventricular enlargement caused compression of pyramidal upper motor neuron fibres in the corona radiate.[3] This however has been questioned by electromyographic evidence showing subcortical involvement by a disturbance in the phased activation of muscles and abnormally increased activity in antigravity muscles.[6,20] Rather, gait ataxia is seen as suggestive of a subcortical motor control issue rather than a pyramidal tract disturbance.[6] Similarly the frontostriatal pathways have been implicated in the development of dementia in iNPH.[4]

Determining Suitability for Shunting of iNPH

Supplemental tests are used to determine the suitability of patients for shunting in the management of iNPH. Testing takes two forms: drainage methods and evaluation by imaging. Identification of patients who improve with CSF drainage may be prognostic in determining a positive outcome following shunt insertion.[22] Commonly used CSF drainage techniques include the TT and ELD.[11] MRI flow studies have been developed and tested with conflicting results.[16] Links have been postulated between aqueductal CSF flow rates and iNPH, with changes in flow being identified following shunting.[23] MRI flow studies looking at overall CSF stroke flow may be of benefit, however prognostic links are yet to be made between aqueductal CSF flow or CSF stroke volume and shunt responsiveness.[16,23]

The TT is the most commonly used diagnostic measure due to its simplicity, short time frame, and easy repeatability. The TT has been shown to be highly prognostic of response to shunting with positive predictive values between 94 and 100% reported, but poor sensitivity between 26 and 61% makes the TT unreliable to exclude response to shunt. One study reported up to 58% of responders to shunting potentially being missed if a TT had been used alone.[9,13] In comparison, ELD has been shown to have sensitivity ranging from 57 to 100% with a positive predictive value of 75–92%.[9,13] Improvement in gait following TT drainage has been demonstrated to occur as early as 30 minutes and up to 24 hours after the intervention.[8] To date, the TT has not undergone any prospective clinical evaluation to determine what might be considered significant improvement in a patient's symptoms.[7,12] While it is agreed that there is a need for measured improvement in gait or cognition following TT, no criterion has been suggested to establish the minimum magnitude of clinically significant improvement.[11] The importance of measured clinical improvement in symptoms underpins the

assumption that improvements measured after TT CSF drainage are likely to be replicated following shunt insertion.[2,18]

External lumbar drainage consists of draining 10 ml/hour of CSF continuously over a period of 72 hours. It was theorized that the increased amount of CSF drainage would result in increased sensitivity and specificity.[3,15] Sensitivity and positive predictive value have been shown to be higher with ELD compared to TT.[15,17] However a lack of validated criteria to determine a positive test outcome also limits ELD. There is increased risk of complications for patients undergoing ELD due to the prolonged period of bed rest required. These include the risk of spinal catheter dislodgement leading to over drainage of CSF.[9] The presence of cognitive impairment might also impair patients' ability to remain flat and idle for 72 hours, impacting on the results of ELD. Another factor that contributes to ELD being used less frequently clinically than TT is the need for hospital admission which adds significantly to the cost of ELD.[13] It is worth noting that to date, no evaluation of either CSF drainage technique has occurred for healthy aged match controls.

Gait Changes in iNPH

Gait changes associated with iNPH have been described as a motor apraxia of gait in the absence of sensory or motor weakness.[5] Analysis of gait patterns before and after shunting has identified changes in velocity, dual stance time, stride length, stance width, and cadence.[5,12] A summary of these changes is provided in Table 2. Similarities have been noted between the gait abnormalities identified with iNPH and those described in Parkinson's disease, namely freezing and shuffling gait.[1,20,24–26]

Guidelines developed in 2005 suggest that for a diagnosis of iNPH, a minimum of two of the following gait features must be present and not attributable to other conditions: decreased step length, decreased step height, decreased cadence, increased trunk sway, widened base of support, out toeing with walking, and *en bloc* turning (turning requiring three or more steps to turn 180°). These abnormal gait signs presenting in patients with iNPH form the basis of physiotherapists' assessment of patients who may benefit from shunting.[12]

Table 2 Gait symptoms currently ascribed to idiopathic normal pressure hydrocephalus (iNPH) in the literature

Study	Symptoms described
Ravdin *et al.*[27]	Narrow base of support Shortened step length Slow turning Tendency for falling Decreased cadence
Stolze *et al.*[26]	Decreased gait velocity Decreased stride length Widened base of support Externally rotated feet Decreased step height
Warnecke[12]	Decreased velocity Decreased cadence Decreased stride length
Williams *et al.*[5]	Increased dual stance time Decreased cadence Decreased velocity Decreased mean velocity

Validation of Upper Limb Coordination Measures, Gait, and Balance Currently used in Patients with iNPH

Standardized tests that are administered by physiotherapists have been postulated to identify improvements in patients' gait and mobility following CSF drainage.[1] Tests that have been suggested to date include the performance orientated mobility assessment (Tinetti), TUG, 10 m walk test, and the nine hole peg test.[1] The Tinetti assessment consists of two components: balance and gait. Scores are combined from the two sections to provide an overall score.[28] The TUG is a measure of the time required for a patient to rise from an armchair, walk to a marker placed 3 m away and return to sitting in the chair. The nine hole peg test is performed bilaterally and measures the time taken for a patient to place nine pegs into a board and remove them again.[29]

The efficacy of upper limb responsiveness to the TT has been investigated. While the nine hole peg test has been identified as one potential option, investigations by Feick *et al.* showed no improvement after three days of ELD, reporting the lack of change may either reflect a lack of change in psychomotor speed over a period of time or poor sensitivity.[1] In an uncontrolled study, potential identifiable improvement with drawing and tracing tasks was described in 42 patients by Tsakanikas.[30] Responders to TT were reported to have significant improvements in upper limb speed and coordination evidenced by a 12% decrease in the time required to trace a prescribed line pattern. Reported sensitivity was 76%, but specificity remained low at 44%.[30] No objective scale was used to quantify perceived improvements or to compare responders. No differences have been identified using other upper limb tests. While results of upper limb testing have been claimed to support their inclusion as part of TT assessment, the lack of efficacy demonstrated in the tracing tasks performed may in fact be due to the floor effect of tests, since many patients are likely to be unable to successfully complete such tests at baseline.[30]

Validation of the Tinetti and TUG to identify change after three days of ELD has been undertaken. Feick *et al.* demonstrated statistically significant change with the Tinetti and TUG in 87 patients.[1] Patients were subject to two days of CSF pressure monitoring followed by three days of CSF drainage at

10 ml/hour. All tests were undertaken before and after drainage. Participants were classified as responders or non-responders to CSF drainage by an expert neurologist. Demographic and tests results were similar between the two groups at baseline. All patients with stable test scores were labelled as non-responders. In responders, TUG time was shown to improve by 15.69 seconds ($P<0.05$), and Tinetti scores improved by 3.21 points ($P<0.001$). Interestingly Tinetti balance scores were shown to have significant improvement in responders after drainage. To date, this is the only evidence related to balance changes after CSF drainage. The Tinetti assessment and TUG therefore appear useful in identifying potential responders to CSF drainage.[1]

The efficacy of the TUG has been questioned by Kubo *et al*. who used the TUG together with cognitive testing to determine the reliability and validity of an iNPH grading scale.[14] Of the 38 patients included in the study, no significant differences in measures of TUG between patients who responded to shunting and those who did not were found. While TUG scores tended to be higher in the 14 shunted patients after the TT, the results were not statistically significant.[14] Analysis of TUG results was not the primary aim of this study and with no reported power calculations related to TUG analysis, extrapolation of results is difficult. A possible explanation proposed by Kubo *et al*. was the TUG is only a measure of walking speed and not fluency of movement, and compared to the proposed iNPH scale, was not as specific in its ability to identify gait changes. However, this explanation is not supported by other authors who have demonstrated identifiable change of TUG results in iNPH after drainage.[1]

Efficacy of computer assisted gait analysis has been explored and demonstrated using the GAITRite portable walkway system.[5] Twenty-eight patients underwent analysis via the GAITRite system after three days of ELD. Fifteen patients underwent shunting, in whom statistically significant improvements were reported in gait velocity, double support time, and cadence. After shunt insertion all measured gait variables had significantly improved. However the commercial links of the author to the system, the equipment space requirements and cost of such a system limits its widespread use in the clinical setting.

The 10 m walk test has been used repeatedly as a measure of gait for iNPH. Rarely has it been used in isolation as an assessment, rather being combined with various scales.[12,14,20,24] Boon *et al*. used the 10 m walk test time combined with step count and walking quality score to quantify the extent of gait abnormality.[20] Individual time and step results were not reported, only combined gait scores, preventing analysis of 10 m walk test results in isolation. Virhammar *et al*. used the 10 m walk test in 40 patients undergoing a TT. Of the 24 responders to the TT, a mean improvement of 5.4 seconds occurred with a mean decrease of six steps being taken over the course.[19]

Owing to their objectivity and repeatability, the validation of tests such as the TUG and 10 m walk test as predictors of TT response is warranted.[19] Argument might also be made for the inclusion of objective balance assessments such as the Tinetti or other balance assessments since they have a proven ability to identify and assess balance and gait dysfunction commonly found in patients with iNPH.[1,5]

The Physiotherapist's Role in Managing Patients with iNPH

Since physiotherapists have expertise in the assessment and management of movement disorders, they are called upon to undertake assessment of patients with iNPH.[1] Typically, physiotherapists assess patients before and after TT to determine any improvements in the patient's parameters of gait and balance. Physiotherapists have trained expertise in gait analysis and are uniquely qualified to accurately measure changes in gait and balance following TT.

Scope for Future Research

While research has been performed validating predictive balance and gait assessment instruments in patients undergoing ELD, no research has looked at validating the instruments' use as predictors of success in patients with iNPH prescribed to undergo the TT. Given the correlation between CSF drainage and shunt insertion, it could be postulated that any measured improvement in a patient's gait following CSF drainage might translate into improvements following shunt insertion. Thus, using validated measures to assess gait and balance outcomes following CSF drainage may assist in the prediction of a positive response to shunt insertion. Establishing the predictive ability of such measures might greatly enhance the determination of patients' suitability for shunting.[12] The current lack of evidence into the extent and existence of balance disturbance within this patient cohort would also indicate the need for further research into this area.

Conclusion

Idiopathic normal pressure hydrocephalus is confounded by a number of diagnostic and management dilemmas. While general consensus exists with regards to diagnostic features and management options, stringent evidence is lacking. The benefit of upper limb testing in assessment for TT response at this stage appears inconclusive with further determination of validated assessments required. There is clear identification of gait abnormalities present in

Table 3 Physiotherapy assessment tools that could be used to assess physical responses in idiopathic normal pressure hydrocephalus (iNPH)

Assessment tool	Information
Berg balance test[31]	14 item balance assessment score out of 56 Validated in stroke
Patient orientated mobility assessment (Tinetti)[28]	2 part assessment scored out of 28 Gait component score of 16 Balance component score of 12
10 m walk test[32]	Time required to walk 10 m distance Validated in ABI, MS, stroke, falls population
Timed up and go (TUG)[33]	Time required to rise from chair with arms walk 3 m around a cone and return to chair Validated in geriatric and stroke population

ABI, Acquired brain injury; MS, Multiple Sclerosis.

iNPH and clear links between gait improvement after CSF drainage and improvement after shunting. Further research is required into identification of balance disturbances in iNPH and the efficacy of balance testing. Evidence is lacking regarding the extent to which gait improvement must occur after the TT to infer a likely response to shunting. Due to the intrinsic nature of gait abnormalities associated with iNPH, instruments that measure gait and balance commonly used by physiotherapists have the potential to provide valid assessments. While a stronger emphasis might be placed on measured gait improvements as a prognostic tool, such instruments should be assessed for their validity and predictive value in patients prescribed CSF drainage as a precursor to shunting (Table 3).

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Conflict of Interest

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Ethics Approval

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Contributors

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ORIGINAL RESEARCH

Gait and Balance Measures Can Identify Change From a Cerebrospinal Fluid Tap Test in Idiopathic Normal Pressure Hydrocephalus

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Abstract

Objectives: To identify in patients with idiopathic normal pressure hydrocephalus (iNPH) undergoing a cerebrospinal fluid (CSF) tap test (TT) for consideration of a ventricular peritoneal (VP) shunt: (1) gait and balance measures, which identify symptom change; (2) differences present between pre− and post−CSF TT scores between patients classified as responders and nonresponder; (3) ability of patients with iNPH to accurately quantify change in their gait and balance symptoms from a CSF TT.

Design: Prospective observational study. Post−CSF TT assessment was completed 2-4 hours post.

Setting: Tertiary referral neurological and neurosurgical hospital.

Participants: Patients (N = 74) with iNPH receiving a 30 mL CSF TT for consideration of a VP shunt.

Interventions: Patients underwent a battery of gait and balance measures pre− and post−CSF TT and indicated their perceived change on a global rating of change (GRC). Patients deemed to improve and offered VP shunt insertion by a neurologist or neurosurgeon were labeled responders.

Main Outcome Measures: Performance oriented mobility assessment (Tinetti), Berg Balance Scale (BBS), timed Up and Go (TUG), 10-meter walk test (10MWT), GRC.

Results: Forty patients were classified responders, 34 nonresponders. Significant differences were identified for responders: Tinetti (3.88 points), TUG (3.98 seconds), 10MWT (0.08 m/sec), and BBS (5.29 points). Significant differences were found for nonresponders for the Tinetti (0.91 points) and BBS (2.06 points). Change scores for responders and nonresponders were significantly different for all tests between responders and nonresponders. GRC scores for gait (+2 for responders, 0 for nonresponders) and balance (+2.5 for responders, 0 for nonresponders) were both significantly different.

Conclusions: The Tinetti, BBS, and TUG can identify change in patients undergoing a CSF TT for iNPH. Patients appear to be able to accurately identify if change has occurred.

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Idiopathic normal pressure hydrocephalus (iNPH) is a reversible form of hydrocephalus presenting with a triad of symptoms composed of incontinence, gait ataxia, and cognitive deficits.[1] This description has formed the basis of iNPH diagnosis for decades but has since been expanded to include balance and upper limb dysfunction.[2-4] Idiopathic normal pressure hydrocephalus differs from other forms in that no obstruction to cerebrospinal fluid (CSF) flow is identifiable and, as such, it is described as a communicating hydrocephalus.[5] Since first described, treatment has remained unchanged. The gold standard of surgical management for all forms of hydrocephalus involves the insertion of a ventricular peritoneal (VP) shunt to drain excessive CSF.[2,4,6] Determining the suitability of surgical management is compounded by difficulty in diagnosing iNPH, which is often done by exclusion of other conditions.[4,7,8] Often patients with provisionally diagnosed Parkinson disease, Alzheimer disease, vascular dementia, or musculoskeletal diseases who fail to respond to treatment undergo further examination to identify an alternate diagnosis.[4,9] However, delayed diagnosis may result in disease progression to a point where treatment is no longer effective. To identify who would benefit from

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surgery, supplemental tests mimicking a VP shunt have been developed.[4,10] Techniques such as external lumbar drainage (ELD) and the CSF tap test (TT) are based on the rationale that symptom improvement from temporary CSF drainage should result in symptom improvement with VP shunt insertion. While ELD requires patients to undergo prolonged bed rest of 3-5 days duration requiring hospital admission, the CSF TT is a simpler procedure and can be completed in an outpatient environment.

The CSF TT is commonly used and involves the removal of 30-50 mL of CSF via lumbar puncture.[9,11,12] Patients are assessed with a range of tests prior to and after a CSF TT to identify symptom improvement. Physiotherapists are routinely involved due to their expertise in mobility and balance assessment.[13-15] Evidence supporting specific outcome measures assessing response to the CSF TT is sparse. Apart from the 10 metre walk test (10MWT), regularly utilized in iNPH studies, no other measures are routinely reported.[11,14] Likewise, the degree of change in patient symptoms that constitute a positive response to the CSF TT has not been established. This results in subjective, inconsistent interpretation of response.[4,9,13] The CSF TT is consistently reported to have high positive predictive value for predicting post VP shunt outcome but poor negative predictive value limiting its ability to exclude patients who will not improve from VP shunt insertion.[11,16] One contributing factor to this may be the lack of consistent application of outcome measures to measure response.

Previous research has determined the validity of several balance and gait outcome measures to identify change from ELD.[14] Feick et al identified that the performance oriented mobility assessment (Tinetti) and timed Up and Go (TUG) could identify significant change in patients undergoing ELD over 5 days with patients deemed to have responded to the procedure demonstrating significant improvement in gait and balance parameters compared to nonresponders. No work of this nature has been completed for the CSF TT despite its extensive clinical use.

This study sought to address three research questions: (1) Which gait and balance outcome measures can identify change in gait and balance symptoms of patients with iNPH undergoing a CSF TT?; (2) Are differences present between pre− and post−CSF TT scores between responders and nonresponders?; (3) Can patients with iNPH accurately quantify change in their gait and balance symptoms as a result of a CSF TT?

List of abbreviations:

10MWT	10-meter walk test
BBS	Berg Balance Scale
CSF	cerebrospinal fluid
ELD	external lumbar drainage
GRC	global rating of change
iNPH	idiopathic normal pressure hydrocephalus
MDC	minimal detectable change
TUG	timed Up and Go
TT	tap test
VP	ventricular peritoneal

Methods

Design

This prospective study of 74 patients was conducted in a tertiary referral neurological and neurosurgical inpatient facility between June 2013 and December 2016. Patients accepted into the study were admitted for investigation of iNPH and scheduled for a lumbar puncture or Rickman's reservoir CSF TT under either a neurologist or neurosurgeon. This study was approved by the Hunter New England Human Research Ethics Committee, reference: 13/06/19/4.02.

Participants

Diagnosis of iNPH was made by the admitting medical officer; a neurologist or neurosurgeon, in accordance with international guidelines.[4,17] All patients admitted for a CSF TT were screened for eligibility. Informed written consent was sought prior to undergoing any pre−CSF TT testing.

Patients were considered for inclusion in the study if they met the following criteria:

- Undergoing a CSF TT for the consideration of a VP shunt for management of iNPH,
- Aged over 55 years in accordance with international guidelines on diagnosis and treatment,
- Ventromegaly present on computer tomography or magnetic resonance imaging with Evans index >0.3 (the ratio of the width of the frontal horns of the lateral ventricles and the maximal width of the internal diameter at the skull).[6]

Exclusion criteria were as follows:

- Patients aged under 55 years,
- Unable to ambulate 10 m with an assistive device,
- Unable to provide informed consent, or no next of kin who could on their behalf.

The use of assistive devices was permitted.

Tap test intervention

The CSF TT was performed by the admitting neurologist/neurosurgeon by either a lumbar puncture or drainage of an implanted Rickman's reservoir. Each CSF TT aimed to drain 30 mL of CSF. Patients were reviewed 1-4 hours post CSF TT by a physiotherapist involved in patient clinical care. This Physiotherapist completed over 98% (71 patients) of testing procedures with the remaining 2% (3 patients) completed by another physiotherapist in their absence. The same physiotherapist administered pre− and post−CSF TT assessments.

One neurosurgeon chose to insert Rickman's reservoirs in lieu of a lumbar puncture due to their longstanding clinical practice. Rickman's reservoirs are a subcutaneous CSF reservoir linked to the lateral ventricles by a catheter. CSF volumes drained and the latency between the procedure and review post CSF TT were the same irrespective of the drainage technique.

Outcome measures

Based upon previous investigation of the CSF TT and ELD, in addition to current clinical practice, a battery of tests were utilized to identify change.[15]

1. BBS
2. Tinetti
3. TUG
4. 10MWT

Table 1 Patient demographics

Characteristics	Study Population	Responder (n=40)	Nonresponders (n=34)	*P* value
Age (y)*	75 (68, 80)	75 (72, 82)	73.5 (64, 80)	*P*=.20
Sex (M/F)	47/27	24/16	23/11	*P*=.39
Symptom duration (mo)	9 (6, 12)	9 (6, 12)	9 (6, 24)	*P*=.30
Time to post−CSF TT assessment (h)*	2 (1.5, 2)	2 (1.5, 2)	2 (1.5, 2.5)	*P*=.45
CSF volume drained (mL)†	29.54±4.31	28.94±5.47	30.24±2.17	*P*=.20
Percent of triad present (gait/cognition/incontinence)	81%/70%/37%	90%/73%/35%	88%/68%/41%	*P*=.72
Number of triad symptoms present 3/2/1	36%/36%/28%	36%/41%/23%	36%/30%/33%	*P*=.17

* Median (interquartile range).
† Mean ± SD.

Each of these standardized measures have been described extensively, utilized widely, and validated in multiple patient cohorts.[18-20] All tests have demonstrated excellent interrater and intrarater reliability.[21,22]

The TUG times how long it takes to rise from a chair, walk 3 metres and return. The 10MWT measures the time taken to walk 10 metres from a moving start.[19,23] The BBS is a 14-point scale assessing static and dynamic balance scored out of 56 points. The Tinetti consists of a balance section assessing 9 items scored out of 16 points along with a gait section assessing 8 items scored out of 12 with a combined score of 28 points.[21,22]

Following the CSF TT, patients were asked to indicate whether they thought there was change in their balance and gait symptoms using a global rating of change (GRC) scale. This is a visual scale with ratings ranging from −5 to +5, whereby −5 is labeled completely worse, 0 labeled no change, and +5 labeled complete improvement.[24] Separate score sheets documented perceived changes in gait and balance. Patients were instructed complete improvement should mean their symptoms had resolved while completely worse meant their symptoms were unmanageably worse.

Determination of response

Results of gait and balance testing were provided to the admitting medical officer along with radiological examination, cognitive examination, and patient reported levels of improvement. These were utilized by the admitting medical officer to determine response status and decide whether surgery should be offered. Five neurosurgeons and 8 neurologists all with between 5 and 30 years specialist experience acted as admitting medical officer for participants. The admitting medical officer after reviewing all available results was responsible for determining the significance of improvement seen across all test batteries. Patients were categorized as responders where surgery was offered, regardless of whether surgery was accepted or declined. Patients not offered surgery were categorized as nonresponders.

Data analysis

Patients were dichotomised into responders and nonresponders for analysis. Within group analysis for responders and nonresponders was undertaken to determine the significance of change within groups with regard to pre− and post−CSF TT scores. Analysis of change scores to determine if differences were present between responders and nonresponders was completed. Significance levels were set at 0.05 for all tests. Spearman's correlation was utilized to calculate correlation coefficients between GRC scales and all outcomes measures. Gait GRC scores were correlated with TUG, Tinetti gait subscore (Tinetti gait) and 10MWT while balance GRC scores were correlated with the Tinetti balance subscore (Tinetti balance), Tinetti, and BBS. As the Tinetti balance subscore is the largest contributor, the Tinetti correlation with balance GRC was used.

Data was analyzed using Stata 13 (StataCorp Tx). Skewness-Kurtosis analysis was completed on all data to assess normality. TUG data was found to not be normally distributed, hence Mann Whitney and Wilcoxon sign rank tests were utilized. T-tests were used for all other data. Chi square tests analyzed differences in sex and triad symptoms between groups.

Sample size for the included outcome measures were calculated using established minimal detectable changes (MDCs).[18,19] A MDC for the TUG was selected from a Parkinson population in the absence of reported MDC in iNPH. The TUG required the highest participant number to identify a statistically significant difference with an MDC of 3.5 seconds and was used for determining recruitment numbers. Based upon a significance value of 0.05 and 80% power, a sample size of 74 patients was required.

Results

Participants

Seventy-seven patients were invited to participate. One patient declined participation and two patients were excluded following a misdiagnosis of iNPH. Seventy-four patients completed pre− and post−CSF TT testing.

Table 1 provides demographic and symptom information. No significant differences were present between responders and nonresponders for the presence or number of triad symptoms. Differences in age and sex between groups were not statistically significant.

Tap test type

Nine patients received a CSF TT via Rickman's reservoir. No significant differences were present for demographics or test scores between CSF TT completed by lumbar puncture or Rickman's reservoir. An average of 29.54 mL of CSF was drained with no between group difference. Median time until post CSF TT review for both groups was 2 hours.

Pre and post tap test scores

Table 2 provides test results for responders and nonresponders. subscores of the Tinetti (balance and gait) are presented.

Table 2 Testing scores pre– and post–CSF TT for all testing parameters

	Responder				Nonresponder				
Test	Pre–CSF TT Median (IQR)/mean ± SD*	Post–CSF TT Median (IQR)/mean ± SD	*P* Value Difference pre/post† (95% CI)	Pre–CSF TT Median (IQR)/ mean ± SD*	Post–CSF TT Median (IQR)/ mean ± SD	*P* Value Change pre/post† (95% CI)	*P* Value Difference pre–CSF TT Score by Response‡ (95% CI)	*P* Value Difference post–CSF TT Score by Response‡ (95% CI)
TUG (s)	18.90 (13.3, 23.10)	14.92 (11.65, 21.90)	**P < .01 (0.54, 8.18)**	17.10 (10.60, 29.60)	16.4 (10.20, 28.30)	P = .69 (-3.19, 2.02)	P = .92 (-7.05, 8.32)	P = .40 (-0.88, 12.05)
Tinetti	10.20±2.98	12.45±4.06	**P < .01 (-2.99, -1.81)**	10.14±4.11	10.56±4.08	P = .15 (-1.00, 0.16)	P = .97 (-1.70, 1.60)	**P = .01 (-3.60, -0.47)**
balance								
Tinetti gait	7.38±2.35	8.90±2.18	**P < .01 (-2.03, -1.02)**	7.59±2.65	8.03±2.76	**P = .02 (-0.80, -0.09)**	P = .71 (-0.95, 1.37)	P = .13 (-2.02, 0.27)
Tinetti	17.65±4.72	21.53±4.11	**P < .01 (-4.68, -3.07)**	17.74±6.42	18.65±6.51	**P = .01 (-1.64, -0.18)**	P = .95 (-2.50, 2.67)	**P = .02 (-5.37, -0.39)**
10MWT (m/s)	0.68±0.28	0.76±0.26	**P < .01 (-0.14, -0.02)**	0.79±0.43	0.80±0.26	P = .63 (-0.05, 0.03)	P = .20 (-0.06, 0.28)	P = .67 (-0.13,0.20)
BBS	35.39±8.57	40.68±7.69	**P < .01 (-6.43, -4.15)**	36±11.81	38.06±12.33	**P < .01 (-3.36, -0.77)**	P = .75 (-4.30, 5.51)	P = .28 (-7.47, 2, 23)

Bold text indicates statistically significant result.
* TUG reported median (IQR); all other tests mean ± SD.
† Nonparametric testing for TUG.
‡ Nonparametric testing for TUG.

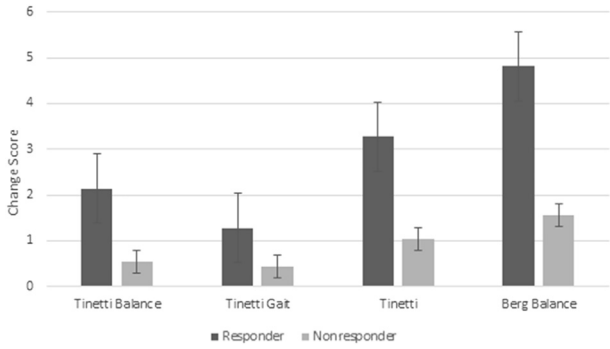

Fig 1 Tinetti, Tinetti Balance, Tinetti Gait, and BBS change score by response.

Significant differences were identified between pre and post scores for responders on all tests. For responders, the TUG identified median change of 3.98 seconds. Tinetti balance showed a mean change of 2.25 points and the Tinetti gait 1.52 points. The Tinetti demonstrated a mean change of 3.88 points and the BBS 5.29 points. The 10MWT showed a mean change of 0.08 ms†. Three tests identified significant pre and post differences for nonresponders: the Tinetti gait (0.44 points), Tinetti (0.91 points), and BBS (2.06 points). No between-group differences existed for any pre–CSF TT scores. Significant between group differences were present in post–CSF TT scores for Tinetti balance ($P = .01$) and Tinetti ($P = .02$).

Significant differences were present for change scores for all outcome measures between responders and nonresponders, the Tinetti ($P < .01$ CI -4.05, -1.88), Tinetti balance ($P < .01$ CI -2.80, -1.17), Tinetti gait ($P < .01$ CI -1.71, -0.43), TUG ($P = .02$ CI -9.47, -0.21), BBS ($P < .01$ CI -4.77, -1.51), and the 10MWT ($P = .05$ CI 0, 0.15).

Figure 1 compares Tinetti and BBS change scores by response, figure 2 TUG change scores by response, and figure 3 10MWT change scores by response.

Global rating of change scores

Table 3 presents GRC scores by response. Responders indicated a median balance change of 2 and 2.5 for gait. Nonresponders indicated a median change of 0 for GRC for both balance and gait. Between-group GRC score differences were significant.

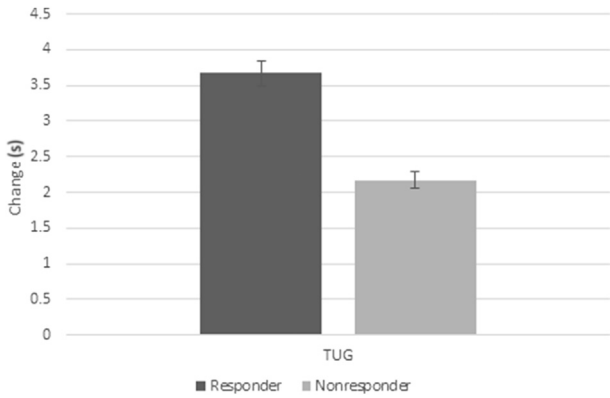

Fig 2 TUG change score by response.

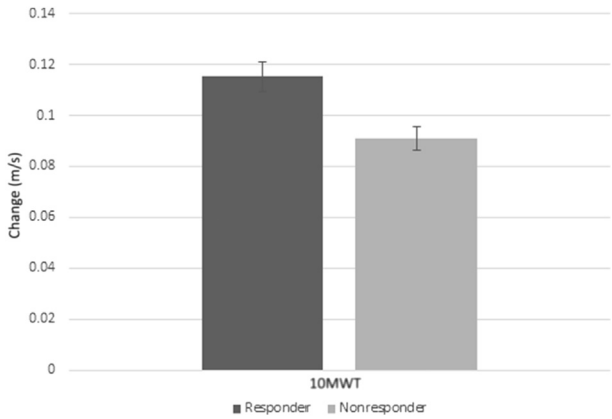

Fig 3 10MWT change score by response.

Change score correlation

Correlation scores for all tests were statistically significant (table 4). Subgroup correlation by response status showed no significant correlations for any test for responders except the BBS ($r=0.35$). Nonresponders showed significant correlation for the TUG ($r=0.36$), Tinetti balance ($r=0.34$), Tinetti ($r=0.42$), and BBS ($r=0.48$).

Discussion

This study provides evidence that several gait and balance outcome measures are useful in detecting change from a CSF TT in patients with iNPH. Significant differences were present between responders and nonresponders for the Tinetti, BBS, TUG, and 10MWT for pre− and post−CSF TT assessments. Responder change scores for all tests, with the exception of the 10MWT, represent scores equal to or larger than established MDCs for these tests, supporting the inference of genuine change.[18-20] Interestingly, significant change was identified for nonresponders for the Tinetti Gait, Tinetti, and BBS. It was deemed that as the change scores for nonresponders were well below established MDCs, while statistically significant, they are not clinically meaningful.

The Tinetti has been previously shown to identify change from ELD and our results suggest that it can also identify change from a CSF TT. Change scores reported from ELD for the Tinetti of 3.21 points are consistent with findings in this study.[14] A four-point mean change for responders is equal with established MDCs for elderly individuals.[20] Comparison of pre- and post-test scores to normative values suggests that there was marked gait and balance impairment in this group of patients.[25] The magnitude of change seen on the Tinetti would therefore support the inference of genuine change being measured by this instrument.

Nonresponder change scores for the Tinetti of less than 1 point could be argued to fall within measurement error. Significant between-group differences for the Tinetti post−CSF TT scores suggest those with a higher score post CSF TT can be identified as likely to be responders. This was also true for the balance subscore. These findings support the ability of the Tinetti to detect response from a CSF TT. When the components of the Tinetti are considered individually, both subscores show significant ability to identify change for responders and nonresponders. Again, the clinical relevance of change for nonresponders can be questioned with mean change scores well below one point, where only full and not half points can be attributed in these tests.

It is only in recent years that balance impairment has been recognized as a significant component of the phenotype of iNPH.[16] The results from this study confirm that balance is affected in patients with iNPH and change can be identified using the BBS. Mean change scores for responders and nonresponders were both significant, however, similar to the Tinetti, nonresponder change scores were below established MDCs indicating an absence of clinical significance.

The TUG is a simple, frequently used test of gait. Minimal equipment requirements, established validity, reliability and normative values, endorse its frequent clinical utilization.[23] Finding statistically significant change for responders supports the use of this test as an outcome measure in iNPH. Nonresponder change scores were neither statistically or clinically significant, further reinforcing the utility of the TUG to discriminate response.

The 10MWT is the most commonly reported test utilized in iNPH research. As with the TUG, the 10MWT is a simple test requiring only a stop watch and walkway to perform. Comparison of 10MWT times to normative values suggests the study sample had moderate gait impairment on admission regardless of responder status.[26] Although the magnitude of change for responders was statistically significant in this sample, test values were below established MDCs for both response categories suggesting that the 10MWT may not be sufficiently sensitive to identify change following a CSF TT.

Participant's perception of change following a CSF TT allows quantification of patient's perception of change in their gait and balance. This would suggest that patients appeared to be able to accurately identify when change had occurred after a CSF TT; however, GRC change scores were only weakly correlated to test results. The BBS was the only test to reveal a significant correlation for responders. For nonresponders' correlation scores were slightly stronger and significant for all tests except the Tinetti Gait subscore. This would suggest that patients appeared to be able to accurately identify when change had occurred after a TT; however, they were unable to either recognize or quantify the extent of this change.

This study utilized a large number of outcome measures to attempt to quantify change. The number of outcome measures that needs to be completed to quantify change has not been explored in this study. It is likely that a smaller number of measures would be

Table 3 Global perceived change scores

GRC	Overall Median (IQR)	Responder Median (IQR)	Nonresponder Median (IQR)	*P* Value (95% CI)
Balance	1 (0, 2.5)	2 (1, 3)	0 (0, 2)	**$P<.01$ (-1.83, -0.56)**
Gait	1 (0, 3)	2.5 (1, 3.5)	0 (0, 1)	**$P<.01$ (-2.22, -0.82)**

Bold text indicates statistically significant result.

Table 4 Correlation scores between test change scores and GRC scores

Test	Overall	Responder	Nonresponder
TUG	**$r=0.33$ $P<.01$**	$r=0.21$ $P=.23$	**$r=0.36$ $P=.03$**
Tinetti balance	**$r=0.32$ $P<.01$**	$r=-0.03$ $P=.84$	**$r=0.34$ $P=.05$**
Tinetti gait	**$r=0.37$ $P<.01$**	$r=0.32$ $P=.07$	$r=0.24$ $P=.16$
Tinetti	**$r=0.47$ $P<.01$**	$r=0.31$ $P=.07$	**$r=0.42$ $P=.01$**
BBS	**$r=0.50$ $P<.01$**	**$r=0.35$ $P=.04$**	**$r=0.48$ $P<.01$**
10MWT	**$r=0.37$ $P<.01$**	$r=0.23$ $P=.19$	**$r=0.37$ $P=.03$**

Bold text indicates statistically significant result.

able to quantify change from a CSF TT. Future work should aim to identify what level of change on these measures is meaningful clinically, and how many outcome measures are required to accurately identify when change has occurred subsequent to a CSF TT. This may facilitate further research to improve the prognostic ability of the CSF TT to predict improvements post VP shunt insertion.

Strengths of this study include the tests utilized are readily available, require minimal training, and are routinely used. The reported use of Tinetti, 10MWT, and TUG in ELD supported their inclusion in the assessment following the CSF TT. This study provides further support for the use of these tests to identify change in performance occurring as a result of a CSF TT for iNPH. Sample size calculations were based on the TUG, which may explain the presence of statistically significant yet small magnitude change scores in nonresponders for the Tinetti and BBS.

Study limitations

A potential limitation to this study is the ability for differences in pre and post scores to be influenced by a learned effect due to the short period of time between completing pre and post testing. While this cannot be excluded from this study design, comparison of change scores for the Tinetti in this study are consistent in magnitude to change scores reported in ELD studies (3.88 vs 3.21 in ELD for responders and 0.9 vs 0.7 in ELD for nonresponders)[14] suggesting that a confounding effect has not occurred. The determination of response to the CSF TT was based on expert medical opinion. This decision, while made by highly qualified medical specialists, may impact the reproduction of these results as there is currently no universally accepted criteria to determine response from these measures in this population.

Conclusion

Statistically and clinically significant change resulting from a CSF TT for patients with iNPH can be detected on assessment of the TUG, Tinetti, and BBS. The 10MWT does not appear to be sensitive to identifying change with change scores below established MDCs. The clinical application of these tests can support clinicians to identify the presence of change from a CSF TT and therefore the suitability of surgical intervention. Patients' identification of changes in their symptoms are consistent with the presence of change identified on objective testing and can be confirmed whether change in symptoms from a CSF TT has occurred.

Keywords

Hydrocephalus; Normal pressure; Physical therapists; Rehabilitation

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Clinimetric Properties and Minimal Clinically Important Differences for a Battery of Gait, Balance, and Cognitive Examinations for the Tap Test in Idiopathic Normal Pressure Hydrocephalus

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BACKGROUND: Idiopathic normal pressure hydrocephalus (iNPH) is treated by insertion of a ventricular peritoneal (VP) shunt. To help identify who would benefit from a VP shunt, patients undergo a tap test (TT). Several measures can identify change from a TT, but the magnitude of change and the combination of measures that indicate the improvement from a TT is unclear.

OBJECTIVE: To develop minimal clinically important differences (MCIDs) for a battery of gait, balance, and cognitive measures in relation to improvement from the TT, and to identify which combination of measures best identifies when improvement has occurred.

METHODS: Observational study of iNPH patients undergoing a TT for consideration of a VP shunt. Patients completed the: The Timed Up and Go (TUG), Timed Up and Go cognition (TUG-C), Performance Oriented Mobility Assessment (Tinetti), and Berg Balance Scale (BBS) pre- and post-TT. A Global Rating of Change scale assessed patients' perceived improvements in gait and balance post-TT.

RESULTS: MCIDs for the TT were (calculated as percentage changes): TUG: 13%, TUG-C: 11% Tinetti: 36%, and BBS: 20%. A combination of the TUG-C and Tinetti resulted in sensitivity of 90.28% to identify improvement, while the Tinetti and BBS resulted in specificity of 98.58% to exclude improvement from a TT.

CONCLUSION: These MCIDs provide the first evidence to quantify the significance of post-TT symptom changes and provides objective data to guide recommendations for clinical management. Utilizing a combination of measures, and these MCIDs as cut off values, results in high sensitivity and specificity for identifying improvement from a TT.

KEY WORDS: Idiopathic normal pressure hydrocephalus, Tap test, Physiotherapy, Neurosurgery

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Idiopathic normal pressure hydrocephalus (iNPH) is a condition characterized by a combination of gait ataxia, balance disturbance, cognitive decline, and urinary incontinence.[1] As the symptoms are similar in nature to Parkinson's disease or Alzheimer's disease, iNPH is typically diagnosed after failure to respond to treatment for these latter conditions.[2-4]

iNPH is often treated surgically by the insertion of a ventricular peritoneal (VP) shunt, a neurosurgical procedure that involves using a catheter to divert cerebrospinal fluid (CSF) from the ventricles of the brain to the peritoneal space in the abdomen.[5-7] Surgical intervention is limited by the fact that not all patients will benefit from surgery, with improvement rates following surgery reported as low as one-third of cases.[6,8,9] Combined with the potential for adverse events postoperatively, efforts to improve the rate of surgical success have resulted in the development of procedures designed to

ABBREVIATIONS: BBS, Berg Balance Scale; **GRC,** Global Rating of Change; **iNPH,** idiopathic normal pressure hydrocephalus; **ICC,** intraclass correlation coefficients; **IQR,** interquartile ranges; **MCID,** minimal clinically important difference; **MDC,** minimal detectable change; **ROC,** receiver operating characteristic; **SEM,** standard errors of measurement; **TT,** tap test; **TUG,** Timed Up and Go; **TUG-C,** Timed Up and Go cognition; **VP,** ventricular peritoneal

temporarily mimic the effects of surgery.[10,11] One such test, the tap test (TT), aims to drain 30 to 50 mls of CSF from patients and assess for symptom improvement. It has been shown that the TT is sensitive to identification of responders to surgical intervention.[4,9,10,12,13]

Which measures should be administered in relation to identifying symptom improvement from the TT is unclear. Similarly, the extent of improvement in symptoms required to suggest a positive result to a TT is yet to be established.[2,14] Previous authors have suggested improvements of 5% or 10% were required to identify a positive response to a TT.[15,16] However, the use of these cut offs to identify improvement is arbitrary and lacking scientific evaluation.

Recent research has sought to identify measures routinely utilized by clinicians to assess gait, balance, upper limb function, and cognition that can identify improvement from a TT.[17,18] It was shown that statistically significant improvements could be identified by the Timed Up and Go (TUG), Performance Oriented Mobility Assessment (Tinetti), Berg Balance Scale (BBS), and 10 m walk test.[17] The 9-hole peg test was unable to identify significant change from a TT while only the sub scores for executive function and orientation of the MoCA identified change.[18] The Timed Up and Go cognition (TUG-C) was able to identify change from a TT with significant differences present between those who improved (labeled responders) and those who did not improve labeled (nonresponders), along with large differences between change scores for responders and nonresponders.[18] Similarly, it was also shown that the TUG, Tinetti, and BBS could differentiate responders to a TT from nonresponders.[17] Patients undergoing a TT were also asked to complete a Global Rating of Change (GRC) scale in relation to improvements in their gait and balance. Responders were able to identify when change had occurred, and where no change was reported this was consistent with nonresponder status.[18] This work, while identifying measures that could identify improvement from a TT, along with quantifying patients' ability to identify change from a TT, did not establish scores for these measures that could be considered sufficient to warrant deeming a patient to have improved from a TT.

A minimal clinically important difference (MCID) is a value that can be used to develop the cut off score by which significant change has been identified by patients and clinicians. An MCID is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in patients management."[19] Given that several gait, balance, and cognitive measures have been identified that can identify improvement from a TT, the magnitude of change for these measures, either singularly or in combination, considered as clinically adequate to confirm a positive response to a TT needs to be established. On this basis this study had two aims: (1) determine MCIDs for gait, balance, and cognitive measures previously identified as able to identify change from a TT; (2) Identify which combination of measures has the best ability to identify when improvement has occurred from a TT.

METHODS

Patients were recruited from a tertiary referral neurology and neurosurgical facility between June 2013 and December 2016. All patients who were admitted with iNPH and aged over 55 yr to undergo a TT were invited to participate. Diagnosis of iNPH was made by the admitting medical officer and consistent with international guidelines on the diagnosis and treatment of iNPH.[3,8] Patients were required to have an Evans index greater than 0.3 on computed tomography or magnetic resonance imaging, and the presence of gait or cognitive or incontinence symptoms consistent iNPH, which were not explained by any other condition.

Written consent was sought from patients after provision of an information pamphlet explaining the study. Ethical clearance to conduct this research was approved in April 2013. Exclusion criteria were inability to walk 10 m with assistance or inability to provide informed consent. Mobility aids were permitted. On enrolment into the study patients underwent a battery of gait, balance, and cognitive examinations before and after undergoing a TT. The following measures were assessed:

- Tinetti
- TUG
- TUG-C
- BBS

The TT was completed by the admitting medical officer and aimed to drain 30 mls of CSF. The above measures were administered by the same physiotherapist pre- and post-TT. On each occasion, patients were given 3 opportunities to complete each measure with the best score of the 3 attempts recorded. Post-TT assessment was completed 2 to 4 h after the TT with the GRC completed immediately after post-TT assessment, prior to patients being informed of TT results. The medical officer completing the TT was blinded to research outcomes.

Patients GRC

Patients marked on a GRC scale the level of change they had noticed in relation to their gait and their balance on completion of post-TT assessment. This scale has been previously utilized as a patient reported measure of change in iNPH.[20] The scale ranges from −5, labeled completely worse to +5, labeled completely improved. Zero was labeled no improvement. Two GRC scales were completed by patients, responding to the questions "with respect to your walking, how much of a change has occurred" and "with respect to your balance, how much of a change has occurred." Patients were additionally guided to compare to their walking or balance immediately prior to undergoing a TT. Patients indicated with a mark on these scales where they perceived change in symptoms were best described. Input from patient's carers when present, was permitted. Patients at times sought input from their carers, which was permitted, to assist in determining a reflective GRC response.

Statistical Analysis

Stata 13 (StataCorp, College Station, Texas) was used for statistical analysis. Sample size calculations for this cohort of patients have been previously reported.[17] A sample size of 74 patients was recruited. Based on a previously reported minimal detectable change (MDC) for the TUG

of 3.5 s, significance levels of 0.05, and power of 0.8, a sample size of 74 patients was determined necessary. The TUG was used as the basis for this calculation as it represented the largest sample size calculation for all measures. Change scores for each outcome were assessed for normality. The TUG and TUG-C were identified as nonparametric.

Prior to MCID calculation, standard errors of measurement (SEM) and MDCs with 95% confidence were calculated for each measure. The formulas used to calculate SEMs and MDCs were used from previously reported methods.[21,22] For the TUG and TUG-C, interquartile ranges (IQR) were used rather than standard deviations. Intraclass correlation coefficients (ICC) were calculated using one-way analysis of variance for each measure.

Minimally clinically important differences were calculated by 2 methods. An anchor-based calculation was completed utilizing GRC scales completed by patients after post-TT assessment consistent with previously published methods.[19] GRC scores were categorized into 4 categories: declined (<0), no improvement (0), moderately improved (0-2), and significantly improved (>2). Mean change scores were calculated for each category for all measures. This established a range for which the MCID for each measure could potentially lie.

A second method utilized receiver operating characteristic (ROC) curves for each measure with GRC scores used as a classifying variable. Anchor-based ROC approaches have been explored in detail for MCID calculation.[23] GRC scores were dichotomized into improved/not improved with cut off scores at 0, >1, and >2. ROC curves were calculated for each level of GRC. MCIDs identified by this method were selected by identifying cut off scores that exceeded the MDC for each measure, represented the best sensitivity and specificity, and were within the ranges developed in method one.

The TUG, TUG-C, and the gait sub score of the Tinetti (Tinetti Gait) were compared against GRC scores for gait, while the balance sub score of the Tinetti (Tinetti Balance), Tinetti, and BBS were compared to GRC scores for balance for both MCID calculation methods. All data were presented as both exact values for the measures and also as percentage change from pre TT scores. These values were calculated independently.

Based on sensitivity and specificity values identified by ROC analysis pooled sensitivity and specificity values were calculated for measure combinations. Calculations were completed on the following combination of measures:

- TUG and Tinetti
- TUG and BBS
- TUG and TUG-C
- Tinetti and BBS
- TUG-C and Tinetti
- TUG-C and BBS

Pooled calculations used formulas based on the completion of measures in parallel. Calculations were completed for both when one measure exceeds a MCID and where both measures exceed MCIDs. Formulas for pooled calculations were used from previously established methods.[24] The highest sensitivity and specificity values for each measure from ROC analysis were used. Sensitivity and specificity values were used from percent change ROC analysis.

RESULTS

A total of 77 patients were approached for this study, and 76 were recruited. One patient declined involvement and 2 patients were later excluded due to a misdiagnosis of iNPH leaving 74 participants enrolled in the study. Sixty-eight patients completed a GRC for their gait and balance. As a result, 68 patients were utilized for this analysis. The TUG-C was included in the TT assessment battery after this study was initiated. Interim analysis of the TUG indicated the addition of the TUG-C would allow adequate effect size for statistical analysis from a smaller sample size then was initially identified. As a result, data are available for 26 patients for the TUG-C.

Demographics

A full demographic description of patients enrolled in this study has been previously reported.[17] The median patient age was 75 (IQR 68, 80), and the median duration of symptoms was 9 mo (IQR 6, 12). Forty-seven patients were male and 27 females. The TT patients underwent drained a mean CSF volume of 29.54 mls (SD 4.31 mls) across all patients with a median time to completing post TT assessment of 2 h (IQR 1.5, 2 h).

Standard Error of Measurement and MDCs

Table 1 provides a summary of ICC, SEM, and MDC for each measure where calculations of exact change values and percentage change values have been reported.

Anchor-Based MCID Calculation

Table 2 summarizes MCIDs from anchor-based calculations. For GRC in gait 3% of patients reported negative change, 37% reported no change, 28% reported moderate improvement, and 32% reported significant improvement. The TUG-C had fewer patients completing this measure with 46% of patients reporting no improvement, 23% moderate improvement, and 31% significant improvement. For GRC change in balance, 3% of patients reported negative change, 35% no change, 35% mild improvement, and 27% moderate improvement.

MCID ranges calculated for each measure were as follows: TUG –26.67% to 5.91%, TUG-C 0% to 20.52%, and Tinetti Gait 16.67% to 39.40%. For the Tinetti Balance the MCID range was 23.86% to 43.57%, the Tinetti 11.89% to 47.45%, and for the BBS 3.33% to 19.81%.

ROC Curve MCID Calculations

Table 3 summarizes MCIDs by ROC curve analysis with sensitivity, specificity, and area under the curves for each measure. Cut off values for each measure remained the same for each category of improvement, creating a range of sensitivity and specificity for these cut off values. MCIDs were selected based on sensitivity and specificity values for each measure. These were: 20% for BBS, 40% for Tinetti Balance, 36% for the Tinetti, 43% points for Tinetti Gait, 13% for the TUG, and 11% seconds for the TUG-C. Figure illustrates the ROC curves for GRC change >1 by measure for exact values.

TABLE 1. ICC, SEM, and MDC Calculations for Individual Assessment Tests

	TUG[a]	TUG-C[a]	Tinetti	Tinetti balance	Tinetti Gait	BBS
Intraclass coefficient	0.94	0.99	0.93	0.76	0.77	0.88
SD/IQR of change score[b] (exact/% change)	4.85 sec/17.62%	3.58 sec/19.36%	2.76/41.55%	1.49/29.13	1.45/33.63%	3.82/22.72%
SEM (exact/% change)	1.19 sec/4.32%	0.39 sec/1.94%	1.35/10.99%	0.73/14.27%	0.54/16.13%	1.32/7.88%
MDC (exact/% change)	3.29 sec/11.97%	0.99 sec/5.38%	3.74/30.46%	2.02/39.55%	2.33/44.71%	3.65/21.84%

[a]IQR used for standard error of measurement calculations.
[b]IQR reported for TUG and TUG-C, standard deviation all other tests.

TABLE 2. MCID Calculations From Anchor-Based Methods for GRC for Balance With Tinetti Balance, Tinetti, and BBS

		GRC of Balance		
Change score	<0	0	0-2	>2
Tinetti balance				
Change score/% change	3.5/43.57	0.42/7.87	1.63/21.48	2.11/23.86
n	2	24	24	18
Tinetti				
Change score/% change	3.5/43.57	0.67/11.89	2.58/31.98	4.17/47.45
n	2	24	24	18
BBs				
Change score/% change	4.50/15	1.17/3.33	3.83/16.75	6.22/19.81
n	2	24	24	18
		GRC of Gait		
TUG				
Change score (sec)/% change	−4.22/−26.67	−0.13/−0.99	1.60/3.29	5.91/5.91
n	2	25	19	21
TUG-C				
Change score (sec)/% change	0/0	1.45/0	2.37/14.60	5.34/20.52
n	0	12	6	8
Tinetti Gait				
Change score/% Change	1.50/16.67	0.24/6.48	0.95/14.71	1.81/39.40
n	2	25	19	21

n, number
Sec, seconds

Pooled Sensitivity and Specificity Values for Measure Combinations

Pooled sensitivity and specificity values for response to the TT for 1 and 2 measures exceeding MCIDs are summarized in Table 4.

DISCUSSION

This study represents the first calculation of MCIDs for measures used clinically in association with the TT in patients with iNPH. This study provides a methodology to support clear cut off values to identify a clinically relevant change from a TT, which would warrant patients being labeled as meaningfully improved following a TT. Outcomes following VP shunt insertion have yet to be addressed by this method, thus the predictive ability of MCID values as they relate to surgical outcomes is not yet known.

Until now, quantification of meaningful change from the TT has been arbitrarily decided. With the development of these MCIDs, patients and clinicians may now have the ability to support decision making related to quantifying improvements from the TT and determining appropriate management for iNPH patients based on the TT outcome. MCIDs have been reported as both exact values and percent changes for the measures utilized. It has been common practice for these measures to have values reported as exact values.[25,26] It is however common place in iNPH literature to determine improvements from a TT based on percent change.[13,27] As such we have focused on drawing conclusions from percentage change values.

TABLE 3. ROC Curve MCID Cut Off Values for Each Test With Sensitivity and Specificity

	GRC balance			GRC gait		
	BBS	Tinetti balance	Tinetti	Tinetti Gait	TUG	TUG-C
MCID (% change)	20%	40%	36%	43%	13%	11%
MCID (exact value)	4	2	4	2	3.63 sec	2.60 sec
Change > 0						
Sensitivity	31.58%	20.00%	50%	17.50%	47.50%	71.43%
Specificity	92.31%	85.19%	81.48%	96.30%	70.37%	75.00%
AUC	0.76	0.68	0.72	0.71	0.66	0.74
Change > 1						
Sensitivity	34.48%	19.35%	58.06%	23.33%	46.67%	72.73%
Specificity	88.57%	83.33%	80.46%	97.30%	64.86%	66.67%
AUC	0.78	0.65	0.70	0.69	0.68	0.75
Change > 2						
Sensitivity	38.89%	22.22%	61.11%	28.57%	57.14%	75.00%
Specificity	84.78%	83.67%	71.43%	95.65%	67.39%	61.11%
AUC	0.74	0.62	0.71	0.67	0.71	0.75

MCID, minimally clinically important differences; AUC, area under the curve

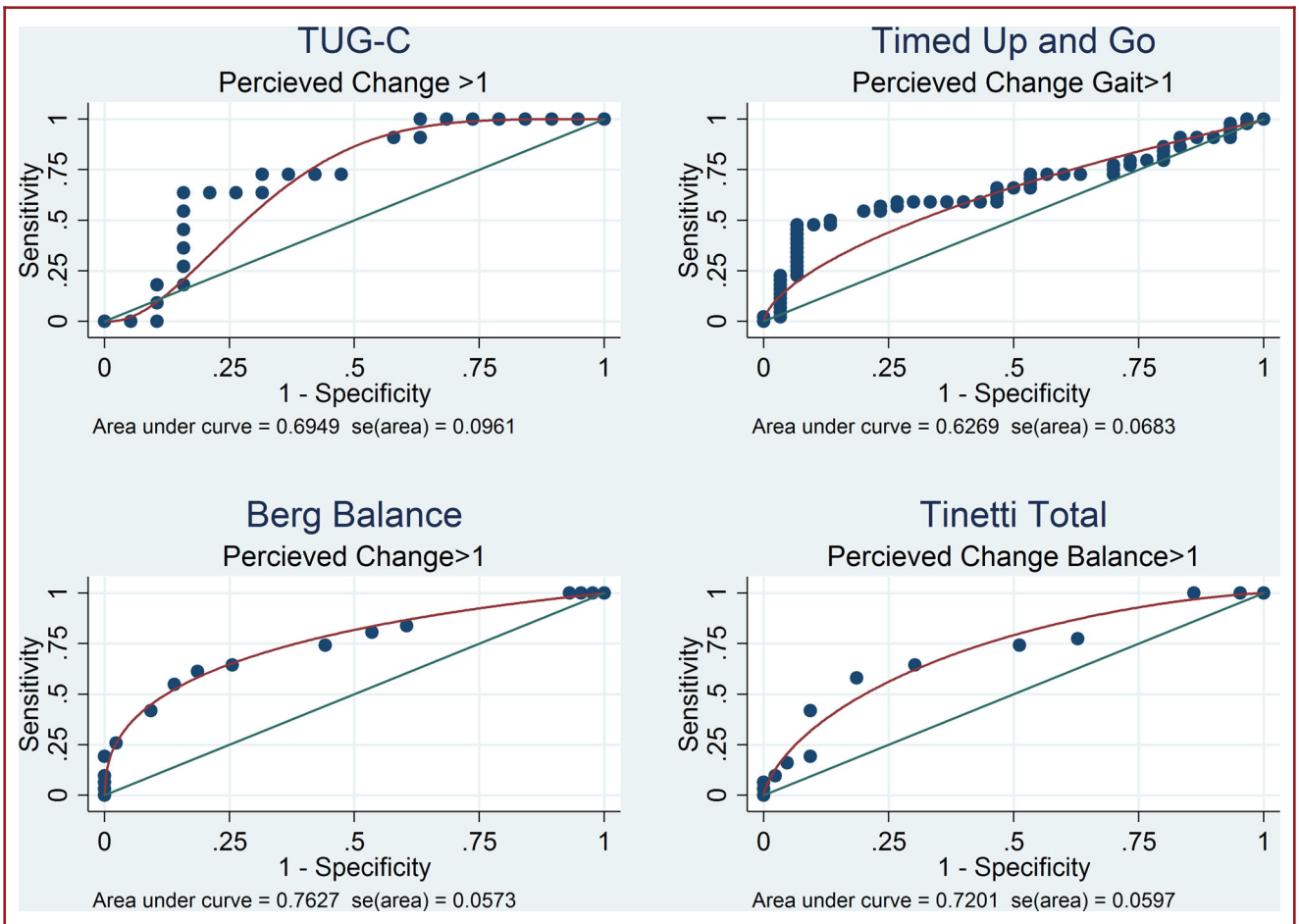

FIGURE. *ROC Curves for TUG, TUG-C, Tinetti, and BBS for exact value at GRC > 1.*

TABLE 4. Sensitivity and Specificity Values for Test Combinations in Parallel

	TUG and Tinetti	TUG and BBS	TUG and TUG-C	Tinetti and BBS	TUG-C and Tinetti	TUG-C and BBS
Sensitivity						
One test	83.33%	73.81%	89.28%	76.23%	90.28%	84.72%
Two tests	34.92%	22.22%	42.86%	23.77%	45.83%	29.17%
Specificity						
One test	59.94%	64.96%	52.78%	75.21%	52.78%	69.23%
Two tests	91.91%	97.72%	92.59%	98.58%	92.59%	98.08%

The use of an anchor-based method to calculate MCIDs ensures that these scores reflect patient's perceptions of the significance of change in their symptoms.[19] Based on the definition of an MCID, values were selected from ROC analysis, which were above our calculated MDCs. In order to recommend patients have sufficiently improved from a TT, potentially making them candidates for VP shunt insertion, clinicians must be certain that the change that has been measured is real, not the result of measurement error, as well as meaningful for patients. The reliance on the GRC as an anchor to quantify MCIDs may be considered a potential limitation due to known issues related to recall bias.[20] Furthermore, the methods for developing MCIDs have been reported as being controversial due to variation in methodology to develop them.[23] In accounting for this, we used 2 recognized methods to identify a range with which a true MCID may fall, combined with the use of ROC analysis to identify specific sensitivity and specificity for selected MCID values to mitigate error. In an attempt to overcome issues of recall bias patients were requested to use a short-term anchor by which to measure any change in their symptoms.

Sensitivity and specificity varied significantly across measures for which MCIDs have been calculated. Sensitivity ranged from 31.58% for the BBS to 75% for the TUG-C. Overall, the TUG-C and TUG represented the measures with the highest sensitivity for identifying improvement in patient's symptoms. Specificity values were highest for the BBS and Tinetti Gait at 92.31% and 97.30%, respectively. The range of sensitivity and specificity of these measures indicates that none of these measures should be considered in isolation and the use of multiple measures would be beneficial to determine when improvement has occurred from a TT. The TUG-C as a standalone measure appears to have the highest ability to rule in or rule out if change has occurred.

The MCID and MDC values for the TUG and TUG-C were not expected. Given that the TUG-C contains a cognitive item in addition to the standard TUG, it would be presumed this measure would have larger values as the TUG-C takes longer to complete. The high ICC for the TUG-C is likely to be a result of the smaller number of patients who have completed the TUG-C compared to the TUG. The high ICC results in a smaller MDC allowing for the selection of a smaller MCID.

Combining measures to determine improvement from a TT results in improvements in the sensitivity and specificity values to identify improvement. It has been previously shown that statistically significant differences are present for self-reported improvement in gait and balance symptoms in regard to improvements to a TT.[17] On this basis, using self-reported improvement to dichotomize patient outcome for the purpose of calculating sensitivities and specificities was undertaken. Pooling of measures is consistent with clinical practice where routinely multiple measures are utilized to identify improvement from a TT. The values calculated in this population will assist clinicians on the most accurate assessment battery to complete with patients undergoing a TT.

A combination of measures that assess gait and balance results in the highest combination of sensitivity and specificity. Combining the TUG-C and Tinetti or the TUG and Tinetti resulted in high sensitivity values to identify improvement from a TT. Utilization of the TUG-C and either the Tinetti or BBS results in similar sensitivity and specificity values. This adds further weight to the efficacy of applying the TUG-C given its additional ability to assess cognitive function through dual tasking while completing a gait task. The TUG has been reported consistently as a measure for assessing improvement in iNPH. Our research suggests that the TUG-C may further enhance the utility of the TUG.

Failure to improve on any 2 measures results in high specificity values between 92% and 99%. This suggests failure to improve by the MCID on any 2 measures is a strong indicator that a patient has not improved following the TT. It has been reported that the TT has low negative predictive value to exclude patients who will improve from VP shunt insertion.[27] These specificity values could suggest that the measures used to identify improvement from the TT may play a role in explaining this low negative predictive value. The assessment regime used and these reported MCID values may result in improved negative predictive values to exclude patients who will not improve from VP shunt insertion.

CONCLUSION

Improvement of 20% for the BBS, 36% for and Tinetti, 40% for the Tinetti Balance, 43% for the Tinetti Gait, 13% for the TUG, and 11% for the TUG-C represent MCIDs for iNPH patients undergoing a TT for consideration of a VP shunt. The use of the TUG or TUG-C with the Tinetti or BBS forms an

effective assessment regime to accurately identify iNPH patients who have improved because of a TT and should be considered for application by clinicians.

Further research is required to identify the extent to which these MCIDs can identify improvement after VP shunt insertion. Research to determine if a predictive ability exists for any of these measures to identify improvements seen following VP shunt insertion will strengthen the clinical relevance of these scores.

Disclosures

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Cognitive and upper limb symptom changes from a tap test in Idiopathic Normal Pressure Hydrocephalus

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ABSTRACT

Objectives: To determine which cognitive and upper limb assessments can identify change in patients undergoing a Cerebrospinal fluid (CSF) tap test (TT) diagnosed with idiopathic Normal Pressure Hydrocephalus (iNPH).
Patients and methods: Prospective observational study of 74 iNPH patients undergoing a CSF TT for consideration of a ventricular peritoneal shunt. Patients who were offered surgical intervention were classified as responders. Patients were assessed with a battery of cognitive and upper limb assessments prior to and following a CSF TT. The Timed up and go cognition (TUG-C), Montreal Cognitive assessment (MoCA) and 9-hole peg test were utilised.
Results: 40 patients were classified responders. Significant differences were identified for responders for the MoCA (0.62 points) and TUG-C (−6.02 s). Only the executive function and orientation sub scores of the MoCA showed significant changes for responders. The 9 hole peg test mean change of 4.33 s for responders was not significant. Non-responder change scores for the MoCA (0.22 points), TUG-C (0.3 s) and 9 hole peg test (2.58 s) were not significant.
Conclusion: The TUG-C has the potential to identify change in patients resulting from a CSF TT. While statistically significant change was found for the MoCA, a mean change of less than 1 point on this scale is unlikely to be clinically relevant. Similarly, the 9 hole peg test cannot be endorsed as an assessment tool for identifying changed performance in iNPH.

1. Introduction

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a condition where patients present with a triad of symptoms of high level gait disorder, incontinence, and cognitive deficits [1]. A neurosurgical procedure, insertion of a ventricular peritoneal (VP) shunt, represents the gold standard treatment [2,3]. This implanted surgical device is designed to divert cerebrospinal fluid (CSF) from the brain ventricles into the peritoneal space. However, not all patients diagnosed with iNPH will benefit [4]. To identify who may benefit supplemental tests have been developed to mimic a shunt [1,3,5,6]. The CSF tap test (TT) aims to temporarily drain CSF [7]. The CSF TT drains between 30 and 60 mls of CSF and patients are assessed prior to and after CSF drainage to determine if changes in symptoms, typically gait and cognition, have occurred [3,7].

iNPH symptoms often overlap or coexist with Parkinson's disease (PD), Alzheimer's disease (AD), or frontal dementia [1,7]. Determining iNPH cognitive deficits opposed to co-existing cognitive deficits can prove difficult [8–10]. Subtle differences have been demonstrated between iNPH and AD with frontal lobe dysfunction disproportionately severe in iNPH and memory impairment distinctly mild compared to matched AD sufferers [8,10,11]. Idiopathic Normal Pressure Hydrocephalus suffers score better orientation and delayed recall testing compared to AD patients but worse on arithmetic and digit symbol substitution tests [8]. Generally the cognitive deficits of iNPH are isolated to executive function impairment [10]. These differences facilitate the ability to assess for cognitive change from a CSF TT.

Extensive evidence supports the prognostic efficacy of the CSF TT to predict positive response post insertion of a VP shunt [4,6,12,13]. However, what degree of change constitutes a positive response and which tests quantify the change resulting from a CSF TT is not clear. Cognitive examination is routinely undertaken to identify patients who may benefit from VP shunt insertion [2,10].

A previous study investigated the Cognitive Assessment of

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Minnesota (CAM) to determine if changes could be identified after external lumbar drainage (ELD), an alternative CSF drainage technique showing it was sensitive in detecting differences between responders and non-responders to surgical intervention [14]. The Montreal Cognitive Assessment (MoCA) is a cognitive examination testing similar domains to the CAM which has been suggested for use in the iNPH population based on its use in other forms of dementia [15]. The MoCA is valid in assessing mild cognitive impairment [16].

Additionally counting backwards from 20 has been evaluated to assess executive function in patients undergoing VP shunt insertion [17]. Counting backwards has been shown to be accurate, valid assessment in iNPH. The Timed Up and Go Cognition (TUG-C) is a test combing a serial counting backwards test with a timed walking task. A combination of the Timed Up and Go with a serial counting backwards task could have potential to aid in identification of surgical candidates. The Timed Up and Go has been demonstrated an ability identify responders v non responders to the tap test previously [18].

Upper limb tests used to measure CSF TT response have been reported in large international iNPH trials [10]. The efficacy of upper limb assessments to detect changes in upper limb performance has been shown by a small body of evidence [19]. Upper limb function testing, using line drawing and tracing tasks, has been investigated to identify change from a CSF TT [19]. The authors suggest that simple upper limb tasks may identify CSF TT responders in addition to traditional gait based assessments [19]. Patients completed a line tracing task before and after a CSF TT. Responders were noted to have an average reduction of 12% in time to complete a tracing task [19]. The 9 hole peg test assesses dominant hand function by measuring the time taken to individually pick up 9 pegs, place them into a 9 slot peg board and remove them again [20]. The 9 hole peg test has been evaluated previously in iNPH and is valid in identifying upper limb dysfunction in PD [14,20]. The 9 hole peg test has been evaluated unsuccessfully previously in an ELD. It was not able to identify improvements in upper limb function from 5 days of ELD [14].

Attempts to identify CSF TT responders varies substantially clinically and within research as many different assessment tools are utilised. Confounding this, no research has focused on defining meaningful change by which a positive response can be identified. Currently arbitrary values of 5 or 10% improvement are listed as signs of positive response [10]. This study sought to answer 2 questions: 1. Identify cognitive and upper limb assessments which can detect change resulting from a CSF TT in patients with iNPH.

2. Identify differences present between patients who respond and don't respond to a CSF TT for cognitive and upper limb assessments.

This information is necessary to streamline and standardise the assessment process currently used by clinicians and to objectively guide decisions regarding patient's suitability to undergo VP shunt insertion.

2. Patients and methods

This prospectiveobservational study was conducted in a tertiary referral Neurological and Neurosurgical facility. Patients admitted to this facility for investigation of iNPH and scheduled to undergo a CSF TT between June 2013 and December 2016 were provided with written information explaining the aims of the study and written consent to participate in the study was sought. This study was approved by the Hunter New England human research ethics committee, reference: 13/06/19/4.02.

Patients were eligible for inclusion in the study if they were admitted for a CSF TT for iNPH, aged over 55 years and diagnosed with Ventromegaly on CT or MRI imaging with Evans index > 0.3. Patients were excluded if they could not walk 10 m with assistance. Mobility aids were permitted. Patients who were unable to consent to the study or did not have a next of kin available to consent were also excluded. Demographic data was collected from patients and their medical records.

2.1. iNPH diagnosis and Pre-Post CSF TT assessment

Diagnosis of iNPH by the admitting medical officer was in accordance with international guidelines on the diagnosis of possible and probable iNPH [2,21].

The Montreal cognitive assessment (MoCA), Timed up and go cognition (TUG-C) and 9-hole peg tests were selected for use based on available research and current clinical practice. The MoCA is routinely used at the participating facility to assess cognitive deficit and was utilised in iNPH prior to the commencement of this study. The TUG-C was selected based on its ability to assess gait and cognitive function.

The MoCA consists of 30 items assessing short term memory, abstraction, executive function, orientation, and language [22]. Three versions of the MoCA exist eliminating learned effect from completing the same test within several hours. Scores below 26 represent mild cognitive impairment and below 21, moderate impairment [16]. The MoCA has been found valid and reliable in PD, AD and cognitive decline [23]. The TUG-C requires patients to rise from a chair, walk 3 m, turn around walk back and sit while counting backwards serially from 100. The TUG-C is a multistep process relying on a level of executive function to correctly execute. The TUG-C has been validated in PD and falls patients [20,21]. The Timed Up and Go has been demonstrated an ability to identify responders v non responders to the tap test previously [22]. The 9 hole peg test is a timed test requiring patients to individually pick up 9 pegs, place them into a board and remove them again.

A Physiotherapist and Occupational Therapist involved in the clinical care of the patient completed the above tests prior to the CSF TT which was conducted by the admitting medical officer (AMO). The assessments were re-administered within 4 h of the CSF TT by the same Occupational therapist and Physiotherapist. Different versions of the MoCA were used on pre-and post CSF TT assessment to eliminate potential for learned affect to confound results.

2.2. Tap test method

One Neurosurgeon inserted Rickman's reservoirs, a subcutaneous CSF reservoir linked to the lateral ventricles by a catheter, to facilitate a CSF TT. Lumbar puncture CSF TT's were completed by all other Neurologists and Neurosurgeons. Each CSF TT aimed to drain 30 mls of CSF.

2.3. Determination of response

Gait, balance, radiological examinations, cognitive and upper limb examinations were provided to the AMO. Patients were classified as responders where the AMO determined improvement in symptoms had occurred across all testing parameters and surgical intervention was offered to the patient. Patients not offered surgery were labelled non-responders.

2.4. Statistical analysis

Patients were dichotomized by response status for analysis. Pre Post scores were analysed by response status. Pre and post CSF TT scores along with change scores were analysed by response status to determine if differences were present.

Stata 13(Statacorp) was utilised for analysis. Skewness-kurtosis testing on data determined if data was normally distributed. Mann Whitney *U* and Wilcoxon sign rank tests were utilised to compare all pre post CSF TT data and demographic data except for the MoCA total where paired *t*-tests were utilised. Chi square tests assessed differences between responders and non-responders for gender and triad symptoms. Significance levels for all tests were set at a $p = 0.05$.

Recruitment numbers for this study were based on power calculations for a separate arm of this research investigating gait and balance

assessments used in association with the CSF TT [18]. A total of 74 patients were recruited.

3. Results

3.1. Demographics

Seventy seven patients were approached, and 76 were recruited as one patient declined involvement. Two patients were later excluded due to a misdiagnosis of iNPH leaving 74 participants enrolled in the study.

Patient demographics have been published elsewhere in detail [18]. The median patient age was 75 and the median duration of symptoms was 9 months. Gait disturbance was the most prevalent triad symptom (81%), followed by cognitive deficits (70%) and urinary incontinence (37%). 36% of patients had all triad symptoms, 36% had 2 symptoms and 28% had 1 symptom.

3.2. Tap test type

Nine patients underwent a Rickman's reservoir CSF TT. No significant differences were present between patients who underwent a CSF TT via lumbar puncture of Rickman's reservoir on any test result or demographic parameter. Median time to completing post CSF TT assessment was 2 h. Median CSF volume drained from patients was 29.54mls, no difference was present between groups ($p = 0.20$).

3.3. Pre Post CSF TT scores

Sixty three patients completed the MoCA, 31 completed the TUG-C and 27 completed the 9 hole peg test. Based on interim analysis results of the MoCA it was identified that additional tests would need to be evaluated to identify cognitive function change from a CSF TT. As a result, the TUG-C and 9 hole peg test were added to the assessment battery after the commencement of the study. Due to this 31 patients completed the TUG-C and 27 the 9 hole peg test.

Table 1 lists results for responders and non-responders. For responders, statistically significant differences were present for the MoCA (0.48 points) and TUG-C (6.02 s). For responders, a median change score of 4.33 s on the 9 hole peg test was not significant. Response status could not be determined based on pre CSF TT scores or post CSF TT scores for any tests.

Median non-responder change scores of 0.22 for the MoCA, 0.3 s for the TUG-C and 2.50 s for the 9 hole peg test were not significant. The MoCA scores of 24 patients regressed on post CSF TT scores. A decline was also seen for eight patients on the TUG-C and 9 hole peg test.

3.4. MoCA sub scores

Table 2 summarises MoCA sub scores by response. MoCA sub score analysis by response showed executive function (1 point change) and orientation (1 point change) change scores were statistically significant for responders. The language change score for responders (1 point) was not significant. No change occurred for naming attention, abstraction or delayed recall.

No significant differences were present for non-responders. Executive function and attention sub scores for non-responders decreased by 1 point post CSF TT. No change occurred for naming, language, abstraction, or delayed recall. 0.5 change for orientation was not significant.

4. Discussion

This study represents the first attempt to quantify the capacity of this battery of cognitive and upper limb tests to identify change resulting from a CSF TT in patients with iNPH. This study evaluated the MoCA, TUG-C and 9 hole peg test to assess changes in cognitive and upper limb performance.

Results for the MoCA are surprising given the established reliability and validity of this test in cognitive impairment [22]. The MoCA has recently been suggested as a test which may be of benefit in neuropsychological testing for iNPH [15]. However, our results would suggest this however is not the case in determining improvement in cognitive function as a result of a CSF TT. Failure for the MoCA to identify cognitive improvement may suggest the timeline to reassessment may not allow for significant cognitive change to occur, or that the MoCA may not be appropriate for application in such a test retest scenario. The MoCA is designed as a brief screening tool by which all domains of cognition may be rapidly assessed. The CAM, which has been shown to identify change from 5 days of ELD, however assesses a wider range of cognitive tasks taking considerably longer to apply than the MoCA. We speculate that the in depth nature of the CAM may be more sensitive in identifying subtle changes which may occur as a result of a CSF TT. Comparison between these 2 tests across these different CSF drainage methods is however difficult. The difference identified in cognitive deficits between AD and iNPH may also have an impact on the MoCA's ability to detect subtle changes. Mean change for responders, while statistically significant, cannot be considered clinically relevant. A change score of less than one point cannot exclude the possibility of measurement errors and is not measurable in an examination. Significant change in sub scores for executive function and orientation fit known cognitive deficits of iNPH suggesting the utilisation of these sub scores of the MoCA could be beneficial. Again, as the change scores are small (1 point for both) the risk of error cannot be excluded. The lack of change in attention sub scores are surprising with no significant differences present between any pre post or responder/non responder

Table 1
Test score pre and post TT for all tests.

Test	Responder			Non-Responder			P Value difference pre CSF TT score by response*	P Value difference post CSF TT score by response*
	Pre TT Median (IQR)/ Mean(SD)	Post TT Median (IQR)/ Mean(SD)	P value difference pre/ post*	Pre TT Median (IQR)/ Mean(SD)	Post TT Median (IQR)/ Mean(SD)	P value change pre/ post*		
Timed Up and Go Cognition (Sec) (n = 31)	23.40(16.60, 26.20)	17.38(12.95, 24.80)	P < 0.01	19.22(13.70, 28.08)	19.52(12.68, 21.92)	P = 0.63	P = 0.42	P = 0.80
Montreal Cognitive Assessment (n = 63)	18.16(4.98)	18.64(5.51)	P = 0.02	19.23(5.17)	19.45(5.22)	P = 0.51	P = 0.42	P = 0.55
9 hole peg test (Sec) (n = 27)	36.53(29, 43.40)	32.20(26.50, 39)	P = 0.14	34(30.20,36.77)	31.42(30.59, 34)	P = 0.51	P = 0.76	P = 0.90

* Non parametric testing utilised for Timed Up and Go Cognition and 9 hole peg test. Parametric tests used for Montreal Cognitive Assessment.

Table 2
MoCA pre and post TT sub scores by response.

Test	Responder			Non-Responder			P Value difference pre CSF TT score by response*	P Value difference post CSF TT score by response*
	Pre TT Median (IQR)	Post TT Median (IQR)	P value difference pre/post*	Pre TT Median (IQR)	Post TT Median (IQR)	P value change pre/post*		
Executive function	2 (1,3)	3 (2,4)	P < 0.01	3 (1,4)	2 (2,4)	P = 0.61	P = 0.28	P = 0.94
Naming	3 (3,3)	3 (3,3)	P = 0.72	3 (3,3)	3 (2,3)	P = 0.45	P = 0.96	P = 0.22
Attention	4 (3,6)	4 (2,6)	P = 0.95	5, (2,5)	4 (3,6)	P = 0.64	P = 0.78	P = 0.78
Language	1 (1,2)	2 (1,2)	P = 0.06	2 (1,2)	2 (1,2)	P = 0.85	P = 0.30	P = 0.97
Abstraction	1 (0,2)	1 (0,2)	P = 0.19	1 (0,2)	1 (1,2)	P = 0.83	P = 0.70	P = 0.45
Delayed recall	1 (0,3)	1 (0,2)	P = 0.43	0 (0,3)	0 (0,1)	P = 0.32	P = 0.38	P = 0.28
Orientation	5 (5,6)	6 (5,6)	P = 0.03	5.5 (4,6)	6 (5, 6)	P = 0.74	P = 0.94	P = 0.54

* Non parametric testing utilized.

analysis. Median scores of 4 for responders and 5 for non responders indicate mild deficits were present in both groups regardless of response status. These however do not appear to be responsive to the CSF TT however. Thirty eight percent of patients recorded a declined in their post CSF TT MoCA scores, which was not anticipated as an improvement or no change was expected.

Findings in relation to the 9 hole peg test are consistent with previous research in ELD and iNPH [14]. When the scores for these iNPH patients are compared to normative values it is evident that upper limb deficits are present. Previously proposed rationales for these deficits is the link to decline in executive function and praxis associated with cognitive deficit from iNPH [19,24]. The 9 hole peg test has been evaluated to identify change in ELD without any success. Its simple time efficient application however warranted its evaluation in relation to the CSF TT [14]. Despite a median 4.06 s change this wasn't statistically significant. It should be noted non-responder median change score of 2.58 s is not largely different to responder change score. This is consistent with previous evaluations [14]. The failure of the 9 hole peg test to register significant change should not preclude further evaluation of alternative upper limb examinations in relation to iNPH.

The TUG-C identified change in responders. The construct of the TUG-C evaluating gait and cognitive ability to count backwards while ambulating is supported by previous research of counting backwards and dual tasking as an assessment item for iNPH. Currently no MDC's have been determined for the TUG-C. Based on established MDC's for the Timed up and it would be reasonable to argue a change of 6 s would exceed a MDC for the TUG-C. The large difference in change scores between responders and non-responders suggests ability to discriminate responders from non-responders.

A primary strength of this study is the investigation of routinely used clinical tests rendering the findings clinically relevant. Potential limitations include the method of determining response status. Currently no gold standard exists for determining a positive response to a CSF TT. This study is reliant on the expert opinion of consultant Neurosurgeons and Neurologists to determine response. Only one test of upper limb function was considered in this study only allowing conclusions to be drawn on this test alone and not upper limb examination in relation to the CSF TT in general.

This study demonstrates the TUG-C is an effective test for identifying change from a CSF TT. Consistent with the findings from alternate CSF drainage techniques used in iNPH the use of the 9 hole peg test to measure change is not supported by this research. Small change scores identified by the MoCA for responders, while statistically significant, cannot be considered clinically relevant. Based on this, combined with significant change only being identified in executive function and orientation sub scores, utilisation of the MoCA to identify change from a CSF TT should be reconsidered. Consideration of alternative cognitive examinations examining executive function and orientation should be considered. Further evaluation of testing focusing on these 2 cognitive domains to identify change would be beneficial in future research in to the CSF TT.

Competing interests

The authors declare no conflicts of interest.

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Author's contributions

Ryan Gallagher contributed to research design, data collection, data analysis and manuscript preparation. Jodie Marquez contributed to research design, data analysis and manuscript preparation. Peter Osmotherly contributed to research design, data analysis and manuscript preparation. Peter Osmotherly and Jodie Marquez are supervisors of Ryan Gallagher PhD candidacy.

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Are gait changes linked to CSF flow changes in the sagittal sinus?

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Abstract

Purpose To identify if specific findings on magnetic resonance imaging (MRI) cerebrospinal fluid (CSF) flow studies can be utilised to identify which patients with idiopathic normal pressure hydrocephalus (iNPH) will have improved gait following a CSF tap test (TT).

Methods Prospective study of patients undergoing a CSF TT for iNPH. Functional gait was assessed using the timed up and go (TUG) test before and after the CSF TT. MRI CSF flow studies accompanied the CSF TT. The minimum clinically important difference for the TUG (3.63 s) was used as a cutoff value to categorise patients as responders to the CSF TT.

Results Fifty-three patients underwent CSF TT and MRI CSF flow studies. Significant differences were identified between groups for (non-responder vs responder) superior sagittal sinus flow (47.10% vs 40.41%), sagittal sinus stroke volume (274 vs 176.5 μl), sagittal sinus to arterial stroke volume ratio (0.203 vs 0.164), sagittal sinus area (42.2 mm^2 vs 36.2 mm^2) and circumference (27.7 mm vs 24.95 mm). No differences were present for aqueduct stroke volume, arterial stroke volume or aqueduct net flow.

Conclusion A link between gait improvement resulting from CSF drainage and sagittal sinus measurements indicates that the sagittal sinus may play a role in the manifestation of symptoms in iNPH. This may have implications for the diagnosis of iNPH and potentially inform clinical decision making regarding surgical intervention.

Keywords Idiopathic Normal pressure hydrocephalus · Sagittal sinus · Gait

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition with a triad of symptoms consisting of gait ataxia, cognitive impairment and urinary incontinence in the context of ventriculomegaly of no identifiable cause [1]. The placement of a ventricular peritoneal (VP) shunt is the gold standard for treatment for iNPH [1–4]. However, treatment success is variable, with a proportion of patients showing no signs of improvement following treatment [5–7]. Studies have shown that as low as one-third of patients who receive a VP shunt demonstrate any improvement in symptoms [2, 6, 8].

Poor rates of treatment response may, in part, be contributed to by the current lack of understanding of the pathophysiology of iNPH and the process by which it manifests [9, 10]. It is thought that iNPH is a form of communicating hydrocephalus where cerebrospinal fluid (CSF) absorption through arachnoid granulations is impaired preventing CSF absorption from the subarachnoid space [3, 11]. This causes CSF volumes to rise and CSF turnover decreases as a result, but no clear mechanism to explain this has been established [12]. One theory related to the development of communicating hydrocephalus supports the elevation of cortical venous pressure as a result of decreased transvenular absorption of CSF from interstitial spaces [13]. It has been suggested that this decreased transvenular absorption alters the pressure gradient between the ventricles and the cortex, decreasing CSF

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absorption and increasing CSF pressure triggering a subsequent increase in cortical venous pressure [13].

Models of pulse wave encephalopathy have been proposed and suggest that a reduction in venous outflow from the cranium results in excessive accumulation of CSF in the subarachnoid spaces and ventricles contributing to iNPH [9]. Other theories propose that arterial hypertension, vascular disease risk factors and diabetes mellitus are a possible reason for increased white matter lesions contributing to the pathogenesis of iNPH [14–16]. Evidence of protein accumulation within arachnoid granulations reducing CSF flow has also been implicated in this condition [17]. Despite multiple theories, the exact mechanisms remain elusive. Research in external and communicating hydrocephalus in children has suggested that elevated venous pressures may contribute to symptom manifestation [18, 19]. Measurements of sagittal sinus pressures have shown an elevation, with the suggestion that these changes may be implicated in the development of hydrocephalus [19]. In paediatric hydrocephalus, obstruction of the sagittal sinus has been shown to result in the development of symptomatic hydrocephalus [18–20]. Idiopathic intracranial hypertension has also been demonstrated to be related to raised venous pressures [18, 21].

Definitive causative links to the symptoms of iNPH have not been established. The venous drainage of the cranium has been proposed as a potential contributor to the development of dementia in iNPH [22]. Bateman in 2002 identified venous compression as a potential cause of dementia in iNPH. He identified that the pulsatility of the superior sagittal sinus was 70% higher in individuals with iNPH compared with healthy controls, and 39–43% higher for individuals with leukoaraiosis [22]. It was concluded that the presence of raised venous pressures across multiple conditions may suggest that a common causative issue may be present across all forms of altered CSF absorption, potentially including iNPH. This could explain the development of dementia symptoms in these conditions. This work did not explore other symptoms associated with iNPH.

To date, minimal investigation of MRI CSF flow has focussed on the role of the venous drainage of the cranium in iNPH, rather focussing on arterial and CSF flow. One study has shown that CSF flow rates through the cerebral aqueduct were 95% predictive for the diagnosis of iNPH [23]. Similarly, it has been shown that stroke volumes greater than 42 μl are a favourable predictor of shunt response [24]. Recent iNPH guidelines concluded that patients with high velocity aqueductal flow on MRI are possibly more likely to improve from shunting [25]. Given evidence of common links between the venous drainage of the cranium and several conditions, along with links shown between changes in the sagittal sinus and the development of dementia in iNPH, there is a need to explore if other symptoms, such as gait changes, in iNPH may be linked to the sagittal sinus.

To allow the identification of potential candidates for VP shunt insertion, various supplemental tests are used [26, 27]. One method, the CSF tap test (TT), a form of temporary CSF drainage, is designed to mimic a VP shunt [10, 28]. This procedure is relatively simple with minimal risk and is used to determine if the more invasive surgical procedure, VP shunt is warranted. Gait is often the symptom most often seen to change from a CSF TT. The rationale underpinning the test is that transient improvements resulting from the CSF TT should be conferred to VP shunt outcomes [29].

Given the previous links drawn between the development of dementia in iNPH and the sagittal sinus, the aim of this study was to determine if differences in measurements of CSF and vascular flow within the cranium on MRI were associated with the improvements in gait following a CSF TT.

Methods

A prospective observational study was conducted in a tertiary referral neurological and neurosurgical facility in Australia from April 2013 to December 2017.

Recruitment

Patients admitted to the facility with a diagnosis of iNPH consistent with international guidelines, for a CSF TT procedure, and who underwent a MRI at the same facility, were invited to participate [3, 30]. Patients were provided with written information detailing study involvement and written consent was sought from the patient or next of kin.

To be considered for inclusion, patients were required to be aged over 55 years, able to walk 6 m with or without a mobility aid or assistance, undergoing an MRI at the participating facility and a CSF TT for consideration of a VP shunt. Patients were excluded if they were ineligible for an MRI or had an MRI completed at an external facility due to inability to collate MRI data from external facilities.

MRI CSF flow studies

All patients were imaged on a 1.5 T superconducting magnet (Avanto; Seimens, Erlangen, Germany). The patients were scanned with standard T1 sagittal, T2 and FLAIR axial images. The MR flow quantification sequence was acquired as a phase contrast study with retrospective cardiac gating. The TR was 26.5 m/s, TE 6.9 m/s, flip angle 15°, slice thickness 5 mm, matrix 192 × 512, FOV 150 and a single excitation. The velocity encoding values were 20 cm/s for the aqueduct flow, 40 cm/s for the venous flow and 75 cm/s for the arterial flow. The plane was selected to pass through the mid portion of the aqueduct for the aqueduct acquisition, to pass from the sagittal sinus 2 cm above the torcular and through the mid part of the

straight sinus for the venous acquisition and along the skull base to pass through the carotid arteries and the basilar artery for the arterial acquisition. The planar imaging, as well as the flow quantification raw data, was archived on the hospital electronic radiology system.

Readings were taken for the following parameters on MRI for flow: aqueduct stroke volume, aqueduct net flow, arterial stroke volume and flow, straight sinus flow, sagittal sinus flow, sagittal sinus stroke volume, sagittal sinus to arterial stroke volume ratio, compliance ratio and sagittal sinus area and sagittal sinus circumference. Using the flow quantification data, regions of interest was placed around the aqueduct, carotid arteries, basilar artery, sagittal and straight sinuses in each patient. Care was taken to exclude aliasing by retrospectively manipulating the base lines of each resultant graph. Background subtraction was utilised to minimise the effect of eddy currents.

The net flow in the aqueduct, arteries and sinuses was derived by the multiplication of the average flow velocity across the region of interest in each for the entire cardiac cycle by the cross-sectional area of the region of interest. The stroke volumes at each site represent the volume increase in fluid/blood which occurs at each site in systole over and above the mean flow i.e. as the flow pulsates, the increase in flow in systole equals the decrease in diastole and the stroke volume represents this change in flow volume. A ratio of the aqueduct stroke volume to the arterial stroke volume comprised the compliance ratio. A similar ratio from the sagittal sinus stroke volume to arterial stroke volume was performed.

The cross-sectional area of the sagittal sinus was measured from the T2 images from a slice selected to be 3 cm above the torcular with both the area and circumference of the sinus measured using the scanners measurement tool. Figure 1 provides a representation of where these measures were taken.

CSF tap test

Patients underwent a CSF TT draining 30 ml of CSF and were assessed using a battery of gait, balance and cognitive assessments before and after the CSF TT. Post CSF TT assessments were conducted within 3 h of the procedure. Patients were asked to complete a timed up and go test (TUG) as part of this assessment battery. The TUG has been shown to be an effective test to identify change from a CSF TT [31]. The TUG requires the patient to rise from a chair, walk 3 m and return to the chair whilst being timed. This was conducted by the same physiotherapist pre and post CSF TT. Patients were given three opportunities to complete the TUG on each occasion with the best time recorded.

Assessor blinding

The neuroradiologist reporting on MRI studies was blinded to all clinical assessments related to the CSF TT, and the physiotherapist completing the clinical assessments was blinded to MRI results.

Determination of response status

Previous research has established the minimally clinically important difference (MCID) for the TUG in iNPH to be 3.63 s [32]. For this study, patients with a TUG change score equal to or greater than the MCID ($\geq$ 3.63 s) were considered to have improved and were classified as responders. Patients with a TUG change score less than the MCID were classified as non-responders.

Statistical analysis

Patients were dichotomised into responders and non-responders based on TUG results for the purpose of analysis. Chi-squared tests were completed on patient demographic data. Skewness kurtosis tests were completed to assess normality. Based on this, the Mann–Whitney *U* tests were used to assess between-group differences.

Response status was used to classify outcomes for ROC curve analysis. ROC curves were developed for all values. Stata 13 (Stata Corp TX) was used for statistical analysis with significance levels set at 0.05.

Results

Nineteen of the 53 patients enrolled in the study were deemed to be responders to the CSF TT, and 34 patients were non-responders. The median time to clinical assessment post CSF TT was 2 h and a mean of 30 ml of CSF drained with no between-group differences in these parameters.

Demographics

A summary of patient characteristics is presented in Table 1. No significant differences were present on any variable except gender.

MRI findings by response to the CSF TT

Between-group differences for MRI measures based on response status to the CSF TT are summarised in Table 2. Significant differences were found between responders and non-responders for superior sagittal sinus flow (SSS) sagittal sinus stroke volume, sagittal sinus to arterial stroke volume ratio, sagittal sinus area and sagittal

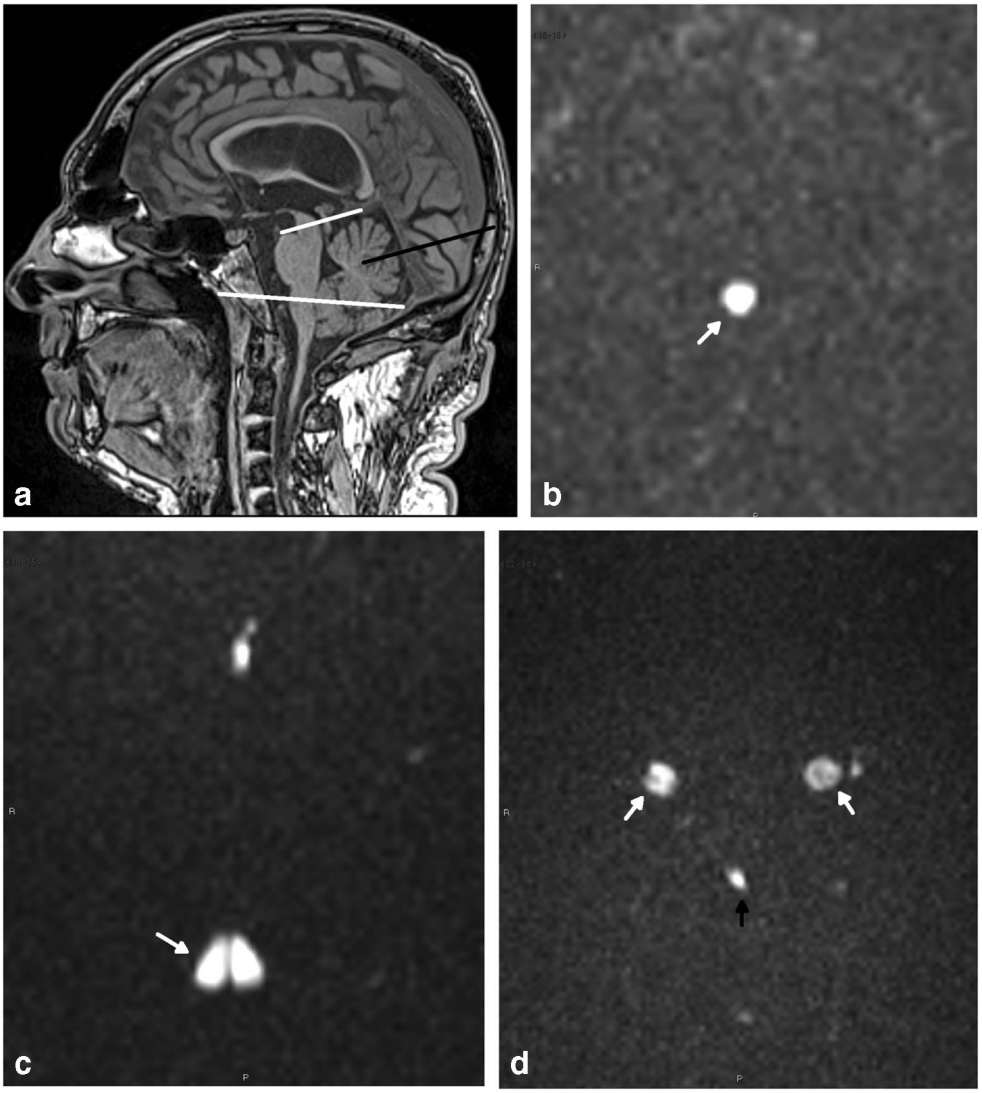

Fig. 1 **a** The sagittal T1 image with the upper white line positioned at the point of the aqueduct acquisition. The black line represents the venous acquisition and the lower white line the arterial acquisition. **b** The aqueduct phase image with arrow showing the aqueduct flow. **c** The venous phase image with arrow showing the sagittal sinus. **d** The arterial phase image with the white arrows showing the two carotids and black, the vertebral artery

sinus circumference. No significant differences were found for aqueduct stroke volume, aqueduct net flow, arterial stroke volume, compliance ratio, arterial inflow or straight sinus flow.

ROC curve analysis and cutoff values

Table 3 summarises AUC, sensitivity, specificity along with positive likelihood ratio (LR+) and negative likelihood ratio

Table 1 Patient demographics by response to the CSF TT

	Study population ($N = 53$)	CSF TT non-responders ($N = 34$)	CSF TT responders ($N = 19$)	P value
Age*	72 (11.80)	72 (8.28)	71 (16.90)	$P = 0.86$
Gender (M/F)	33/20	23/12	10/8	$P = 0.03$
Symptom duration* (months)	10.5 (6,12)	10.5 (6,18)	10 (6,12)	$P = 0.61$
Time to post CSF TT assessment*	2 (1.5, 2.5)	2 (1.5, 2.5)	2 (1.5, 3)	$P = 0.09$
Time from MRI to CSF TT* (days)	38 (1107)	35 (1,87)	74 (1203)	$P = 0.36$
CSF volume drained (ml)	30 (4.9)	29.73 (4.59)	29.06 (5.54)	$P = 0.66$
Percent of triad present (gait/cognition/ incontinence)	92/83/45	89/80/46	100/89/44	$P = 0.80$
Number of triad symptoms present 3/2/1 (count)	23/19/11	14/12/9	9/7/2	$P = 0.46$

*Results median (IQR) all other results mean (SD)

Table 2 MRI values by CSF TT response

MRI value (median (IQR))	CSF TT non-responders ($N = 34$)	CSF TT responders ($N = 19$)	P value for between-group difference
Aqueduct stroke volume (μl)	140 (96, 200)	145 (60, 200)	$P = 0.80$
Aqueduct net flow (ml/s)	0.003 (− 0.01,0.02)	0.010 (− 0.009, 0.05)	$P = 0.18$
Arterial stroke volume (μl)	1342 (943, 1666)	1183 (943, 1420)	$P = 0.31$
Arterial flow (ml/s)	8.65 (7.37, 9.62)	9.38 (8.43,9.97)	$P = 0.07$
Straight sinus flow (ml/s)	1.26 (1.05, 1.57)	1.23 (1.16, 1.44)	$P = 0.93$
Sagittal sinus flow (ml/s)	4.16 (3.29, 4.69)	3.62 (3.32, 4.23)	$P = 0.32$
Superior sagittal sinus (SSS) flow (%)	*47.10 (40.65, 53.62)*	*40.41 (37.08, 47.20)*	*$P = 0.04$*
Sagittal sinus stroke volume (μl)	*274 (178, 412)*	*176.5(153, 270)*	*$P = 0.02$*
Sagittal sinus to arterial stroke volume ratio	*0.203 (0.153, 0.283)*	*0.164 (0.125, 0.183)*	*$P = 0.02$*
Sagittal sinus area (mm^2)	*42.2 (39.5, 49.2)*	*36.2 (31.4, 41.8)*	*$P < 0.01$*
Sagittal sinus circumference (mm)	*27.7 (25.24, 30.4)*	*24.95 (23.1, 25.8)*	*$P < 0.01$*

Italicized entries represent statistically significant result

(LR−) for CSF TT results. Figure 2 illustrates the ROC curve for the sagittal sinus area and Fig. 3, sagittal sinus circumference.

Discussion

This study has identified consistent findings related to the improvement in gait from CSF drainage via a CSF TT and measurements of the sagittal sinus. No research to date has identified any findings related to the sagittal sinus, iNPH and a link to change in gait symptoms. Previously, research implicating the sagittal sinus' involvement in iNPH has drawn links to dementia symptoms of iNPH [22]. This research now shows evidence that changes in the sagittal sinus are implicated in the development of two of the triad of symptoms in iNPH. The consistency of our findings adds additional evidence to the hypothesis that the sagittal sinus has some implication in iNPH physiology and its measurement may have an important clinical and prognostic role.

Previous research has focussed on the role of the cerebral aqueduct in terms of flow as a diagnostic marker and potential prognostic tool in identifying iNPH [23, 33, 34]. We did not find any difference in aqueduct flow between responders or non-responders for a CSF TT. This appears to be consistent with recent research questioning the use of aqueduct net flow to identify shunt responsive iNPH [33].

This exploratory analysis highlights that patients with iNPH who respond to CSF drainage have lower values on almost every measurement taken for the venous system and higher for every value of the arterial system. While not all of these measurements were statistically significant, the consistency of these findings could suggest that pathology of the vasculature of the cranium may contribute to iNPH. Previous research has shown links between changes in vascular dynamics, specifically hypertension and iNPH [14]. However, the findings of this study provide a more detailed link between vascular dynamics and improvements in gait symptoms suggesting that there is compression of the sinuses as indicated by the sagittal sinus area and circumference changes and maybe an increase in the transmural pressure accompanying this.

When considering superior sagittal sinus flow, it appears that the sinuses are much more non-compliant in those who see gait improvement from a CSF TT. The higher values recorded for those who do not see gait improvement could suggest that greater flow through the sagittal sinus negatively impacts the effectiveness of CSF drainage techniques.

Table 3 Cutoff values and clinimetric values for MRI measurements

Measure	Cutoff value	Sensitivity	Specificity	AUC	LR+	LR −
Superior sagittal sinus flow (%)	38.6	82.86%	44.44%	0.67	1.49	0.39
Sagittal sinus stroke volume (μl)	173	80%	50%	0.71	1.6	0.40
Sagittal sinus to arterial stroke volume ratio	0.164	74.29%	50%	0.69	1.49	0.51
Sagittal sinus area (mm^2)	37.2	91.43%	55.56%	0.75	2.06	0.15
Sagittal sinus circumference (mm)	24.81	82.86%	44.44%	0.75	1.49	0.39

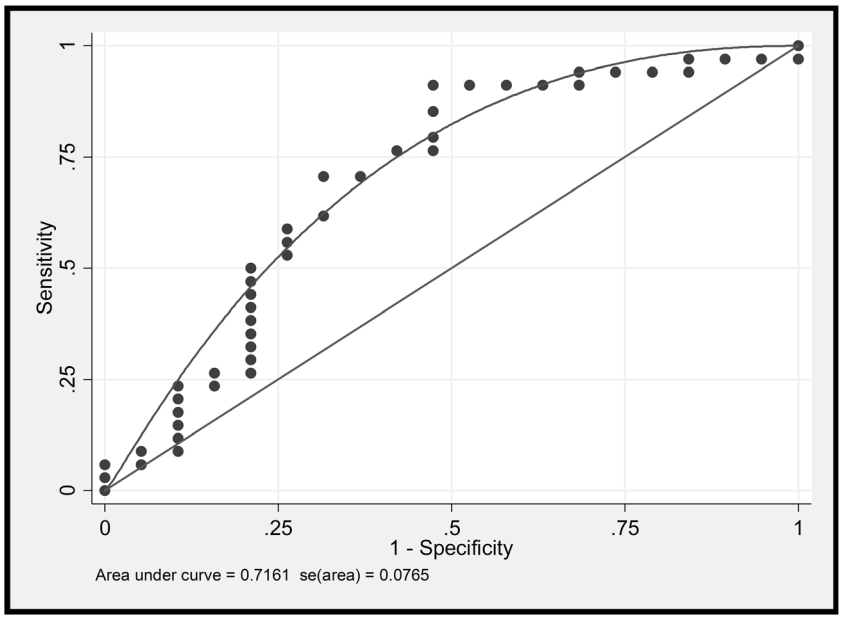

Fig. 2 Sagittal sinus area ROC curve

Similarly, it may suggest patients who demonstrate clinical improvement in gait may have cranial vascular changes which are less severe or yet to develop to the same degree as those who do not respond.

ROC curve analysis demonstrates that sagittal sinus area, flow and circumference can successfully identify improvements in gait resulting from CSF drainage. The AUC for sagittal sinus area and sagittal sinus circumference combined with high sensitivity and specificity values at the selected cutoff values indicates these measures have the ability to identify whether patients will experience gait improvements following CSF drainage. The AUC of other MRI measures suggests these tests are not useful in determining gait improvements from CSF drainage.

Sagittal sinus area, flow or circumference is not currently used measures to identify iNPH. Recent research has concluded that the sagittal sinus outflow resistance must be significant in the pathophysiology of other forms of hydrocephalus [19]. This research suggests these findings are also present for iNPH. In the presence of evidence now implicating the sagittal sinus in relation to dementia and gait symptoms in iNPH, this would add weight to support the hypothesis that the sagittal sinus changes may be related to iNPH causation and warrants further investigation.

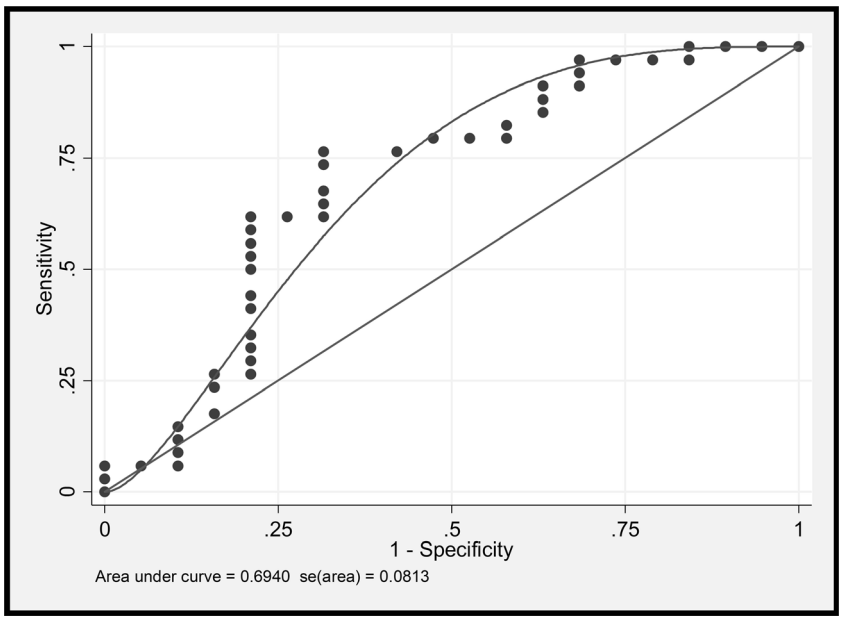

Fig. 3 Sagittal sinus circumference ROC curve

The findings in relation to sagittal sinus measures and patients who respond to CSF drainage are logical in relation to the flow of CSF. Any restriction related to the flow of CSF in the venous system will result in a flow on effect throughout the CSF circulation within the cranial vault. These changes may not be large in scale but over a time could result in significant changes in the flow of CSF and result in adaptive changes to a rising volume of CSF.

The possible effect of confounders in this study cannot be excluded due to the research design and the large number of measures analysed. However, despite these limitations, the findings are consistent across the CSF TT and confirmation with further research is warranted. Additional research is required to determine if the results of this research exist after VP shunt insertion.

Conclusion

The findings of this study provide additional evidence indicating changes in CSF flow through the sagittal sinus and the size of the sinus are altered in iNPH and implicated in the development of symptoms of iNPH. Furthermore, the extent to which changes occur in the sagittal sinus may provide the opportunity to differentiate patients who will experience gait improvements from CSF drainage as opposed to those who will not. Whether these changes in the sagittal sinus are as a result of or causative of iNPH is not clear from these findings.

Further research to confirm these findings post VP shunt are warranted in addition to further work regarding the role of the sagittal sinus in iNPH. Findings suggest that changes in the sagittal sinus may be associated with the development of iNPH and may be used to assist diagnosis and predict response to treatment of iNPH patients into the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Hunter New England Human Research Ethics Committee approved this study. All participants gave written informed consent prior to data collection beginning. Reference: 13/06/19/4.02.

Informed consent Informed consent was obtained from all individual participants included in the study.

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A46

Can upper limb and cognitive outcome measures identify change in patients undergoing a lumbar puncture tap test with idiopathic normal pressure hydrocephalus (INPH)?

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Introduction: The lumbar puncture tap test (TT) is regularly utilised to identify shunt responsive iNPH. Testing regimes aim to identify change in function but vary significantly. This study aimed to determine if a battery of upper limb and cognitive outcome measures can identify change in iNPH patients undergoing a TT.
Methods: Prospective cohort study of 74 patients undergoing a TT diagnosed with iNPH. Patients performed the Timed up and go cognition test (TUG-C), 9-hole peg test, and Montreal Cognitive Assessment (MoCA) before and after a TT. A Neurologist determined response status, patients who improved were labelled as responders. Sign-rank tests were used to analyse between groups differences.
Results: Forty patients were categorised as responders, 34 non-responders. For responders, the median change in the TUG-C (− 6.02 s $p < 0.01$) and MoCA (0.62 points $p = 0.02$) was significant. Only executive function and orientation sub scores of the MoCA showed significant change (1 point each, $p = 0.03$). The median 9 hole peg test change (4.33 s $p = 0.14$) was not significant. For non-responders changes of 0.22 points for the MoCA ($p = 0.51$), 0.3 s for TUG-C ($p = 0.63$) and 2.58 s for the 9 hole peg test ($p = 0.51$) were not significant.
Conclusions: The TUG-C can identify change following a TT and should be considered for use. Change on the MoCA, of less than 1 point, cannot be considered clinically significant. Further investigation is required regarding the ability of sub scores of the MoCA to identify change. The 9-hole peg test cannot identify change and cannot be recommended.

A47

Can gait and balance measures identify individuals who respond to a lumbar puncture tap test in patients with idiopathic normal pressure hydrocephalus (INPH)?

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Introduction: The lumbar puncture tap test (TT) is a common test to identify shunt responsive iNPH. Varying testing regimes are used to identify change but specific tests are not supported by evidence. This study sought to determine if a battery of gait and balance outcome measures can identify change for patients with iNPH undergoing a TT.
Methods: A prospective cohort study of 74 patients undergoing a TT. Patients were assessed before and after a TT using the: 10 m walk test, Timed up and go (TUG), Tinetti assessment, and Berg Balance Scale (BBS). Patients deemed to have improved by a Neurologist were labelled as responders. Between group differences were analysed with sign-rank tests. Change scores were compared to established minimal detectable changes (MDC's) for these tests. Sample size calculations were based on established MDC's for the TUG.
Results: Forty patients responded, 34 were non-responders. For responders, significant change was identified for the TUG (3.98 s $p < 0.01$), Tinetti (3.88 points $p < 0.01$), Berg (5.29 points $p < 0.01$) and 10 m walk (0.08 m/s $p < 0.01$). For non-responders significant change was identified for the Tinetti, (0.91 points $p = 0.01$) and Berg, (2.06 points $p < 0.01$). For responders, the 10 m walk change fell within established MDC's, for non-responders, all change scores fell within established MDC's.

Conclusions: This research provides the first evidence to support specific tests which identify change following a TT in iNPH. The TUG, BBS and Tinetti can identify change. The 10 m walk test does not appear to be sensitive to identify change with change scores below established MDC's.

A48

Is the sagittal sinus involved in idiopathic normal pressure hydrocephalus (INPH). Analysis of MRI CSF flow studies in patients undergoing a CSF tap test

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Introduction: The lumbar puncture tap test (TT), routinely used to identify shunt responsive iNPH, is limited by low negative predictor values. MRI CSF flow studies are often utilised in conjunction with a TT to improve identification of shunt responsive iNPH. This study aimed to identify what markers on MRI CSF flow studies which can identify change in gait from a TT.
Methods: Prospective cohort study of 42 patients undergoing a TT and MRI CSF flow studies. Patients completed a timed up and go (TUG) test before and after a TT. The minimum detectable change (MDC) score for the TUG was used as the cut off value. Sign-rank tests were used to evaluate between groups differences.
Results: 17 patients improved on the TUG, 27 did not improve. Signifi t between group differences were found for (no improvement vs. improved): sagittal sinus circumference (26.60 mm vs. 24.89 mm $p < 0.01$), sagittal sinus area (41.6 mm^2 vs. 34.4 mm^2 $p < 0.01$), sagittal sinus stroke volume (225 µl vs. 172 µl $p = 0.04$) and superior sagittal sinus fl w percentage (47.77% vs. 38.83% $p = 0.03$). No differences were present for aqueduct stroke volume (140 µl vs. 140 µl $p = 0.57$), aqueduct net fl w (0.002 ml/s vs. 0.08 ml/s $p = 0.21$), arterial infl w (8.29 ml/s vs. 9.31 ml/s $p = 0.21$) or compliance ratio (7.94 vs. 12.71 $p = 0.45$)
Conclusions: A link between improvement in gait symptoms and sagittal sinus measurements indicates that the sagittal sinus may play a role in the manifestation of symptoms in iNPH. This may also have a role in diagnosis of iNPH. Further research is required to confirm the significance of these findings.