Ultra-low pressure hydrocephalic state in NPH: benefits of therapeutic siphoning with adjustable anti-gravity valves

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jonathan Funnell, Linda D'Antona, and Claudia Craven. The first draft of the manuscript was written by Jonathan Funnell and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abstract

Background

Idiopathic Normal Pressure Hydrocephalus (NPH) is a condition of the elderly treated by ventriculoperitoneal shunt (VP) insertion. A subset of NPH patients respond only temporarily to shunt insertion despite low valve opening pressure. This study aims to describe our experience of patients who benefit from further CSF drainage by adding adjustable anti-gravity valves and draining CSF at ultra-low pressure.

Methods

Single-centre retrospective case series of patients undergoing shunt valve revision from an adjustable differential pressure valve with fixed antigravity unit to a system incorporating an adjustable gravitational valve (Miethke proSA). Patients were screened from a database of NPH patients undergoing CSF diversion over 10 consecutive years (April 2008 – April 2018). Clinical records were retrospectively reviewed for interventions and clinical outcomes.

Results

Nineteen (10F:9M) patients underwent elective VP shunt revision to a system incorporating an adjustable gravitational valve. Mean age 77.1 ± 7.1 years (mean ± SD).

Eleven patients (58%) showed significant improvement in walking speed following shunt revision. Fourteen patients/carers (74%) reported subjective improvements in symptoms following shunt revision.

Conclusions

Patients presenting symptoms relapse following VP shunting may represent a group of patients with ultra-low-pressure hydrocephalus, for whom further CSF drainage may lead to improvement in symptoms. These cases may benefit from shunt revision with an adjustable gravitational valve, adjustment of which can lead to controlled siphoning of CSF and drain CSF despite ultra-low CSF pressure.

Keywords

Cerebrospinal Fluid

Gravitational valve

Low Pressure Hydrocephalus

Normal Pressure Hydrocephalus

Shunt revision

Ventriculoperitoneal shunt

Abbreviations

CSF: Cerebrospinal Fluid

NPH: Normal Pressure Hydrocephalus

VP: Ventriculoperitoneal

Introduction

Idiopathic Normal Pressure Hydrocephalus (NPH) is a condition of the elderly characterised by progressive gait disturbance, often accompanied by cognitive impairment and/or urinary incontinence[19, 23, 31]. Typical imaging findings demonstrate ventriculomegaly in the context of normal cerebrospinal fluid (CSF) pressure[2, 19, 23, 31]. The mainstay of treatment for NPH is neurosurgical, involving the shunting of CSF away from the subarachnoid space, most commonly by ventriculoperitoneal (VP) shunt[22, 27]. Outcomes of surgery are frequently tested through assessment of walking speeds and stride length which improve with CSF drainage, however shunting has also been shown to improve quality of life of NPH patients and is a cost-effective intervention[7, 10, 21].

CSF drainage by VP shunting is controlled by incorporating a valve into the shunt that opens and closes at a set opening pressure. Differential-pressure valves open when the pressure gradient across the valve exceeds the opening pressure set on the valve. Gravitational valves are open by design when the patient is horizontal, however when the patient is in the upright position will require a set pressure gradient across the valve to open. They were developed mainly to prevent siphoning of CSF in the upright position, a phenomenon produced by the effects of hydrostatic pressure in the water column produced by VP shunts.[16, 30]. Consequences of overdrainage remain some of the commonest complications of shunted NPH and can be associated with significant morbidity[12, 25, 27].

Arguably one of the more significant developments to shunt technology has been to introduce valves with adjustable opening pressures, which allow for post-operative adjustment of CSF outflow. Adjustable gravitational valves have been proposed as a solution to the management of complex hydrocephalus patients, in whom there is a delicate balance between sufficient CSF drainage and developing complications[11].

Short and long-term outcomes of shunting in NPH tend to be positive, with many patients showing sustained response following CSF shunt[4, 22, 27]. Some patients however initially respond to CSF diversion but subsequently deteriorate despite post-operative adjustment of their shunt valve setting[1, 9]. A subset of patients show clinical response to drainage by way of a CSF tap test suggesting that further CSF drainage would be beneficial. This drainage may not be possible with valve adjustments alone as the low intra-ventricular pressure

is insufficient to overcome the resistance of a high pressure antigravity valve, even with ultra-low opening pressures on a differential pressure valve[15, 28] As a result, our practice is to revise the shunt system to incorporate a proSA adjustable gravitational valve (Miethke, Potsdam, Germany) and reduce the opening pressure to drain further CSF in the upright position, leading to controlled siphoning of CSF.

The aim of this observational case series is to evaluate the effectiveness of revising VP shunts to include an adjustable gravitational valve in NPH patients with delayed post-shunt deterioration. Additionally, we discuss management of low pressure state following CSF diversion in the NPH population.

Methods and materials

Study design

This study is a single-centre retrospective observational case series. A series of NPH patients who temporarily responded to VP shunting before developing further progressive NPH symptoms is described. The study is reported with reference to STROBE guidelines.

The study inclusion criteria were as follows: (i) diagnosis of idiopathic NPH treated with VP shunt; (ii) patent VP shunt; (iii) revision of the VP shunt system from one incorporating a fixed gravitational valve to one incorporating an adjustable gravitational valve. Eligible patients were identified from a clinical database of NPH patients undergoing CSF shunting over a consecutive period of 10 years (April 2008 – April 2018).

This study excludes patients undergoing revision as a result of shunt blockage or mechanical obstruction of normal shunt function. Patency was assessed pre-operatively by clinical examination and imaging (shunt series X-rays and computed tomography), and in theatre at revision.

Follow-up and outcomes of patients were evaluated retrospectively from clinical records until May 2019.

NPH management

Patients assessed for probable NPH underwent a standardised walking test, diagnostic imaging, and a diagnostic trial of extended lumbar drainage. Patients showing an objective clinical improvement were offered VP shunting with an adjustable differential pressure valve (Miethke proGAV/proGAV 2.0) at 5cmH2O opening pressure, and a fixed gravitational valve (Miethke ShuntAssistant) at 25cmH2O opening pressure. Clinical improvement was assessed by comparing walking test times before and after intervention(s). A standard 10-metre walking test was used to assess walking speed, depending on the performance status of the patient. An improvement is locally defined as an increase in walking speed by 10%, or reduction in number of steps needed to walk 10 metres by 10%. Patient and carer-reported symptoms were assessed at interview with a consultant neurosurgeon, or clinical nurse specialist in hydrocephalus.

In patients presenting with delayed post-shunt deterioration, an assessment is made whether the patient would benefit from further CSF drainage. In the first instance, adjustments to shunt valve settings are made to lower the opening pressure. To test for further benefit, a shunt tap test may be performed. This is performed by puncturing the shunt reservoir with a 23-gauge butterfly needle and withdrawing 20-40 mL of cerebrospinal fluid. A 10-metre walking test is performed before and after the tap test and clinical improvement assessed.

Improvement following tap test is indicative that patients will benefit from further CSF drainage, assessed by walking test or if patients report a clear improvement in symptoms. Increase in walking test speed or decrease in number of steps required to walk 10 metres by 10% indicates improvement. For patients whom improvement is identified, a shunt revision is offered following counselling of the risks and potential benefits. **Fig. 1** provides a simplified representation of this centre's management of a typical patient with NPH who may benefit from shunt revision with an adjustable gravitational valve (proSA).

Shunt revisions

In cases requiring shunt revision, the shunt system patency was confirmed intra-operatively by disconnecting the shunt system proximally, with free CSF flow expected. Distal end patency was tested using manometry.

Since the introduction of the proSA valve to our centre in 2013, this has involved explanting the fixed gravitational valve (ShuntAssistant at 25cmH2O) and replacing this with an adjustable gravitational valve (proSA, initially at 20cmH2O). In the earlier cases in this series, the adjustable differential-pressure valve was also replaced with a fixed differential-pressure valve (Miethke miniNAV at 5cmH2O), however in later cases the adjustable differential-pressure valve was left in situ.

Clinical outcomes

Patients with NPH at our centre are routinely followed-up long term following VP shunting. Due to the observational nature of this case series, a fixed endpoint was not used. Length of follow-up was determined by time from revision until most recent assessment in clinic at time of data collection.

As with investigations, walking test improvement following surgical intervention is locally defined as an increase in walking speed by 10%, or reduction in number of steps needed to walk 10 metres by 10%. Following shunt revision, this is compared with the walking test time prior to shunt tap test (or pre-revision in patients not undergoing this investigation). For the purposes of this study also, patients were determined to have improved if they reached this threshold of improvement at walking test during follow-up. Serial walking test results were used to establish the best adjustable valve setting, as in clinical practice.

Statistical analysis

The following data was collected for each patient: age, sex, dates of birth, VP shunt insertion and revision, serial walking tests and valve settings, and last follow-up. Serial walking test results were collected at the pre-shunt, post-shunt, pre-revision (or pre- and post-tap test), post-revision stages and following valve setting changes. Patient and carer-reported outcomes were also recorded.

Continuous variables were summarised as means (±standard deviation) and categorical variables as percentages. Walking test speeds were presented as medians and ranges. Wilcoxon matched-pairs signed-rank tests were used to compare the pre and post intervention walking test speeds of the patients. A significance level 0.05 was used. Microsoft® Excel for Mac (version 16.25) and Stata© (version 15.0) were used for the data collection and statistical analysis.

Results

Demographics

The clinical database identified 213 patients who underwent CSF diversion at our institution for NPH between April 2008 and April 2018 (211 VPS, 2 LPS). Of these, 46 patients had undergone shunt revision. Thirty-eight patients underwent a CSF tap test for assessment of subacute deterioration not responding to VP shunt adjustment, of whom 28 subsequently underwent revision.

Nineteen patients (10F : 9M) with NPH satisfied our inclusion criteria by undergoing elective shunt revision for delayed post-shunt deterioration, using the proSA valve. Seventeen patients underwent revision of both shunt valves (proGAV + ShuntAssistant) to a fixed differential pressure valve (miniNAV) with proSA. Two patients underwent revision of gravitational valve only (ShuntAssistant replaced with proSA, proGAV left in situ). The first included revision took place in May 2014. Mean age of patients undergoing revision was 77.1 ± 7.1 years (mean ± SD). Patients were followed-up for an average of 27 ± 19 months (mean ± SD) following shunt revision.

Clinical presentation

All patients had undergone trials of shunt valve adjustment prior to revision. Thirteen patients (68%) had low shunt opening pressures (<5cmH2O), 4/19 (21%) had a shunt opening pressure the same as when originally implanted (5cmH2O), and 2/19 (10%) had high shunt resistance (>5cmH2O) – both of whom experienced low pressure symptoms when shunt opening pressure was reduced.

Eighteen patients (95%) underwent revision at least 1 year after initial VP shunt insertion. Average time from initial VP shunt to revision was 33.9 ± 15.8 months.

Pre-shunt revision tap test

Seventeen patients underwent a tap test to assess for benefit of further CSF drainage. One patient underwent a CSF infusion study without walking test to check shunt function. One patient did not undergo any invasive investigations between VP shunt and revision.

Among the 17 patients who underwent tap test, 14 (82.4%) showed objective improvement in mobility. In the remaining 3 patients, a lack of improvement had been attributed to a normal walking speed pre-tap, however these patients reported subjective improvement in walking and balance at interview. Objective improvement was noted for 2 patients however the walking test speeds were incompletely documented therefore not included in numerical analysis. There was a significant improvement between pre- and post-tap walking test speed (Wilcoxon matched-pairs sign-rank p=0.003) with a median speed difference of 22.6% (median % of speed improvement, range: -4.0 – 51.1).

Post-shunt revision outcomes

Eleven patients (58%) showed a significant improvement in mobility following revision, at the best valve setting. Ten of those showed an improvement in walking test time compared to pre-tap walking test (or pre-operative in patients not undergoing tap test), one patient improved from being wheelchair bound to walking, although still unable to complete 10m. Clinical outcomes of participants in this case series are summarised in **Table 1** alongside participant characteristics, and pre- and post-revision valve settings.

Of mobile patients with documented walking speeds at the pre-tap, and post-revision stages in clinic (n=10), walking test times significantly improved by 25.7% (median % of speed improvement, range: -12.0 – 56.5%, Wilcoxon matched-pairs sign-rank p=0.04). Of these patients, those judged to have improved did so by 31.3% (median % of speed improvement, range: 22.6 – 56.5%) (n= 6). Median (± range) 10-metre walking test results at different stages of the patients' clinical history are displayed in **Fig.2** (post-shunt, before and after shunt tap test, and following shunt revision).

Fourteen patients (74%) and/or their carers reported subjective improvements in mobility or cognition following revision, at the best post-revision valve setting.

Complications/re-interventions

Three patients in this series (15.8%) required return to theatre. One patient developed surgical site infection, requiring removal of shunt less than 3 months post-revision. One patient required a further shunt revision, to remove a fixed differential-pressure valve and replace this with an adjustable differential pressure valve. This patient showed further improvement following second revision. One patient underwent externalisation, and re-

internalisation of the shunt due to further deterioration despite adjustments to adjustable anti-siphon device. This patient subsequently showed improvement at walking test.

Two patients died within 6 months of shunt revision of unrelated causes.

Discussion

Low pressure state in Normal Pressure Hydrocephalus

This study focuses on the clinical course of a group of patients with NPH that show only a temporary response to CSF drainage at low opening pressures (with a fixed gravitational valve). Subsequent subacute deterioration, and improvement following negative pressure drainage (as produced by a tap test) are features in keeping with low pressure hydrocephalus – a phenomenon described in some patient populations following VP shunting[13, 17, 20, 29].

Low pressure state in idiopathic NPH is an especially complex situation, in part due to the impaired compliance of parenchyma as part of the disease process, which can be seen on ICP monitoring [2, 5, 6] We did not observe this group of patients to be significantly different from out database of patients treated for NPH, however it could be proposed that patients with low pressure state are more susceptible to developing a state of impaired compliance during ventricular dilatation prior to CSF diversion.

The results following further CSF drainage by tap test, and subsequent improvement with low gravitational valve opening pressures offer proof-of-principle that negative pressure drainage may be necessary for therapeutic drainage in these patients[20, 29]. By reducing the opening pressure of these valves, controlled siphoning of CSF is allowed, and negative pressure in the shunt system is generated when patients are upright.

An alternative theory underlying the low-pressure state in NPH is more closely related to the development of NPH and disordered cerebral blood flow (CBF) autoregulation[24]. Salma proposes that the first stage in the pathogenesis of NPH is a drop in cerebral blood flow, noted to be reduced in NPH and the restoration of which is associated with positive outcome[18, 24, 26]. As per the Monro-Kellie doctrine, a drop in intracranial blood volume should be matched by a compensatory increase in CSF volume, causing hydrocephalus at low pressure[24].

An emerging option in management of complex NPH?

This single-centre case series reports a group of patients who initially respond to CSF drainage, however despite low valve opening pressures do not drain sufficient CSF by VP shunt[1, 9]. This suggests that a subset of NPH

patients have very low intraventricular CSF pressure, who require controlled siphoning of CSF to achieve optimum drainage. These patients can be identified by a tap test from the VP shunt, and at time of data collection was managed with exploration of the shunt and if patent, explantation of the shunt valves and replacement with an adjustable antigravity valve. It is particularly important to differentiate these patients from those with NPH-like longstanding overt ventriculomegaly (LOVA), who may also not respond to CSF diversion in the same way as NPH, and who will significantly overdrain with further CSF drainage[3].

In this case series, 58% of patients showed a significant improvement in mobility, and a greater proportion of patients or their carers reported subjective improvements in symptoms (74%). By using a similar treatment algorithm, Gutowski et al. showed that implanting an adjustable antigravity valve improved symptoms in 46% of patients with delayed post-shunt deterioration[9].

The balance between sufficient drainage to optimise symptoms while preventing overdrainage symptoms is delicate[12, 30]. CSF overdrainage symptoms, and development of subdural collections remain some of the commonest complications of VP shunting, especially when a low-pressure differential pressure valve is used[8, 12, 27]. Implantation of an antigravity valve can help reduce the risk and allow the opening pressure of the differential pressure valve to be reduced to safely drain more CSF[8, 28]. Adjustable valves develop this further, by allowing post-operative adjustment of the amount of resistance needed, either to drain more CSF or to conservatively manage overdrainage complications[16, 25, 30]. Furthermore, implantation of an adjustable anti-gravity valve has been shown to be as safe as an adjustable differential pressure valve[11].

Two patients in this series illustrate this in particular, who experienced overdrainage symptoms with their original VP shunt necessitating increased resistance in the adjustable differential pressure valve. These patients subsequently showed benefit from increased CSF drainage by pre-revision tap test, although only one of these two showed an improvement following revision with adjustable antigravity valve. No complications of overdrainage were observed in this series, demonstrating that further CSF drainage with low opening pressures in the upright position can be safely achieved in low pressure hydrocephalus.

As a result of our experience with adjustable gravitational valves and availability of a new valve (Miethke M.blue plus), we have modified our standard treatment protocol for idiopathic NPH to incorporate an adjustable

antigravity valve in new VP shunt systems. By incorporating both an adjustable differential pressure unit, and adjustable antigravity component, this system is hoped to suit a range of patients with different valve setting needs, including those with ultra-low pressure. We hope to evaluate whether this will lead to better functional outcomes, fewer complications (by avoiding overdrainage), and fewer revisions with more flexibility in post-operative adjustment. In future, it is hoped that significant developments will be made in shunt valve technology in the search for a "smart" shunt system, which offers this flexibility with automated adjustment of shunt opening pressures to suit each patient and detection of complications[14].

Limitations

This case series has two obvious limitations: it is small and retrospective. Our primary outcome was measured walking speed, which can be affected by a number of other conditions and does not take into consideration the cognitive and urodynamic effects of NPH. Furthermore, at some points several patients were unable to complete the walking test or required varying amounts of aid which meant we were not always able to quantify the amount of improvement or deterioration between points in time.

Conclusions

VP shunting with adjustable differential pressure valves alongside a fixed gravitational valve may not drain sufficient CSF in a subset of patients with ultra-low pressure NPH. These patients present with subacute deterioration following CSF shunting, and improve following CSF tap; suggesting a symptomatic low-pressure hydrocephalic state that requires ultra-low opening pressures to drain sufficient CSF. This can be achieved with a low-pressure differential pressure valve in line with a low-pressure anti-gravity valve, which allows for controlled siphoning of CSF from the ventricles and can be adjusted post-operatively to tailor to each patient's needs.

Revision with an adjustable gravitational valve may improve outcomes in this small subset of patients, however in view of their safety our practice has moved towards implanting these valves as part of new VP shunt systems. We look forward to evaluating the impact this has had on patient outcomes, and on the high revision rate currently seen in shunt surgery for NPH.

Declarations

Conflicts of interest

No funding was received for the conduction of this study. LD's research fellowship is sponsored by B.Braun. LDW has received honoraria from and served on advisory boards for Medtronic, B.Braun and Codman. AKT research time was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The other authors have no disclosures to report.

Ethical standards

All procedures performed in 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. For this type of study formal consent is not required. Informed consent was given by all patients for procedures described as part of their routine clinical management.

Figure legends

Fig. 1 Flow chart showing typical management of idiopathic NPH at this centre leading to shunt revision with an adjustable gravitational valve (proSA)

Fig. 2 Median 10- metre walking test results of the patients following initial VP shunt insertion, pre- and post-shunt tap test (TT), and following VP shunt revision

Table 1. Demographics, valve settings and outcomes of included patients

Pt. #	Sex	Age at revision	Pre-revision valve setting (cmH2O)		Best post-revision valve setting (cmH2O)		Mobility outcome	Subjective outcome
			DP valve	Grav. valve	DP valve	Grav. valve		
1	M	67	2[a]	25	5	15[a]	Improved	Improved
2	M	75	5[a]	25	5	16[a]	Improved	Improved
3	F	72	5[a]	25	5	20[a]	Improved	Improved
4	M	71	1[a]	25	5	20[a]	No improvement*	Improved*
5	M	67	2[a]	25	5	16[a]	Improved	Improved
6	F	94	5[a]	25	5	20[a]	Shunt removed*	Shunt removed*
7	M	76	1[a]	25	5	10[a]	Improved	Improved
8	F	83	0[a]	25	0[a]	20[a]	Improved	Improved
9	F	71	2[a]	25	5	20[a]	Improved	Improved
10	F	81	2[a]	25	5	14[a]	Improved*	No improvement*
11	F	84	3[a]	25	5	17[a]	Improved	Improved
12	F	72	6[a]	25	5	15[a]	Improved	Improved
13	F	72	6[a]	25	5	15[a]	Improved	Improved
14	F	79	10[a]	25	5	16[a]	Died	Died
15	M	71	1[a]	25	5	20[a]	No improvement	Improved
16	M	86	3[a]	25	5	20[a]	Died	Died
17	F	77	5[a]	25	5	16[a]	Improved	Improved
18	M	71	0[a]	25	5[a]	15[a]	No improvement	Improved
19	M	76	1[a]	25	5	16[a]	No improvement	No improvement

([a]) = adjustable valve
(*) = returned to theatre

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