Review Article

Idiopathic Normal Pressure Hydrocephalus: Correlating Magnetic Resonance Imaging Biomarkers with Clinical Response

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Abstract

Idiopathic Normal Pressure Hydrocephalus (NPH) is a debilitating condition of the elderly. The patient is typically "wet, wobbly and wonky", to different degrees of the triad. The diagnosis is supported by the radiologic finding of dilated ventricles, determined by an elevated Evan's Index (EI) without a demonstrable cause. Patients with newly diagnosed NPH typically respond to ventriculo-peritoneal shunting (VPS). NPH-related dementia is possibly the only surgically reversible dementia. An elevated cerebrospinal fluid (CSF) flow rate (FR) is associated with a positive response to shunting. However, post-shunting EI and FRs are unpredictable. Of late, intracranial apparent diffusion coefficient (ADC) quantification via Diffusion Weighted Imaging (DWI) has been emerging as a possible marker in NPH diagnosis. A local study, conducted on a national level, to study the relationship of EI, FR and ADC to pre- and post-shunt clinical measurements has just ended. This review seeks to reconcile the current thinking of NPH, magnetic resonance imaging (MRI) quantification and clinical evaluation, and in the process shed some light on major pathophysiological determinants of the disease.

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Key words: Apparent diffusion coefficient, Cerebrospinal fluid flow dynamics, Modified total improvement index, Peak flow rate

Introduction

Idiopathic Normal Pressure Hydrocephalus (NPH) is a condition of the elderly. First introduced in 1965, it is typified by urinary incontinence, gait disturbance and cognitive decline.[1,2] We refer to it as the "Wet, Wobbly and Wonky" Syndrome.

Despite numerous debates in the ensuing 43 years since it was first described, its exact cause is still unclear. Enthusiasm has been shown for theories ranging from the water hammer pulse[3-5] to deep white matter ischaemia[6,7] to decreased compliance of the superficial veins.[8]

Because NPH-related dementia is possibly the only surgically reversible dementia, unlocking its pathophysiology could represent a major breakthrough in terms of the application to reversing other dementias. As such, investigators continue to agitate for a deeper understanding as to its aetiology.

What is widely accepted is that patients with newly diagnosed NPH typically respond to ventriculo-peritoneal shunting (VPS).[9,10] How shunting reverses the dementia and other symptoms of hydrocephalus are still unclear. An understanding of this reversal will shed light on how other forms of dementia can be reversed.

Conventional diagnostic investigations have relied on computed tomography (CT) derived Evan's Index (EI), intracranial pressure (ICP) monitoring and cerebrospinal fluid (CSF) infusion tests.[3,11-14] The latter 2 tests are invasive and costly. Their reliability and reproducibility is also limited.[15] Magnetic resonance imaging (MRI) poses an attractive alternative to these tests because of its non-invasive nature. Also, unlike CT, it is non-ionising as well and is highly suited as a research tool.

This paper serves to discuss the expanding role of MR imaging in hydrocephalus. It will also update the reader on where we stand locally and how local data is helping to shed light regarding the aetiology of NPH as well as how shunting reverses its symptoms.

The Emerging Role of MRI in NPH

1. Anatomical Evaluation via Cross-sectional Imaging

The finding of dilated ventricles is defined via the EI, which computes the maximal frontal horn ventricular

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width divided by the transverse inner diameter of the skull. Ventriculomegaly is defined as a reading of 0.3 or greater.[16] EI is a key diagnostic marker of NPH.[12,13] However, there has been no clear cut relationship between clinical improvement post-shunting and a decrease in ventriculomegaly.[12,17-19] This absence of a positive correlation leads us to suspect that ventriculomegaly is a symptom (often irreversible) rather than a cause of the syndrome.

Other reported determinants of hydrocephalus severity on conventional cross sectional imaging include small cortical sulci (less than 1.9 mm) and periventricular hypodensity on CT[12] or periventricular T2 hyperintensity on MRI.[20]

2. Functional Evaluation

MRI has followed after CT in providing grey scale appreciation. It has also gone the extra step in developing quantitative biomarkers.

(A) CSF Flow Dynamics

Proposals for indices of shunt response first appeared in 1991 with Bradley reporting a correlation between a marked CSF flow void within the aqueduct and a good response to ventricular shunting.[14] This was followed by 2 landmark papers reporting on the use of CSF flow rate (FR) as a quantifiable marker for shunt response.[21,22] Several studies have since attested to the FR's value in shunt response prediction.[23,24]

The FR is captured at the level of the cerebral aqueduct using prospective cardiac gating Phase Contrast (PC)-MRI. The level of interest is centred to the inferior colliculus, perpendicular to a line drawn through the distal aqueduct on the sagittal scout (Figs. 1 & 2). All patients were scanned on a 1.5T MRI scanner (Signa, General Electric, Milwaukee, WI, USA). Typical scanning parameters are TR/TE: 19/8 msec, FA= 20˚, section thickness = 7 mm, matrix = 256 x 128 matrix, FOV = 16 cm, Venc = 20 cm/s, flow compensation and 16 cardiac phases via peripheral gating. The data is then processed via a flow analysis programme on a GE Advantage Windows workstation (General Electric, Milwaukee, WI, USA) offering computation of flow velocity (in cm/sec), flow rate (in mL/min) and stroke volume (in μL).

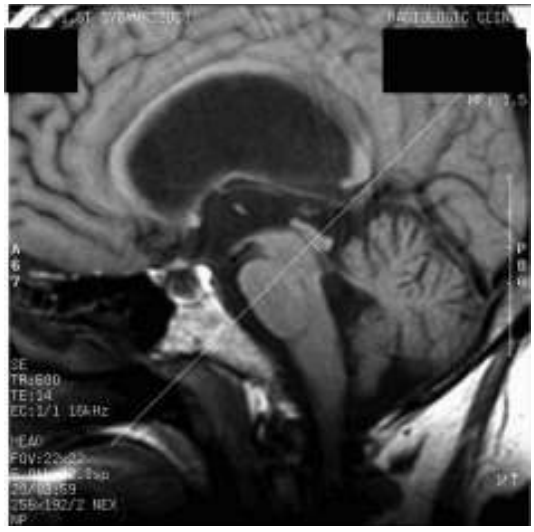

Fig. 1. The level of interest is centred to the inferior colliculus, perpendicular to a line drawn through the distal aqueduct on the sagittal scout.

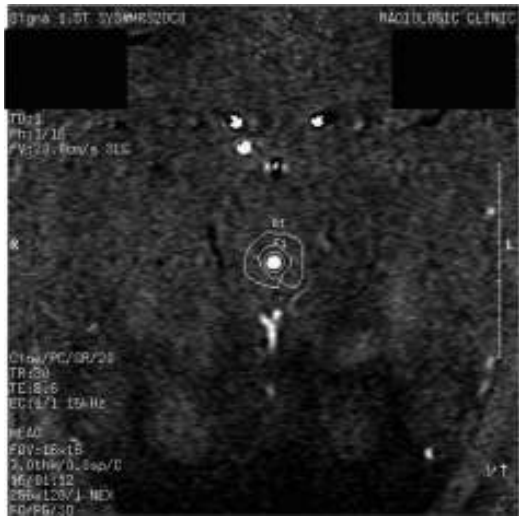

Fig. 2. Axial section, at the level of interest, where the region of interest (ROI i.e. the cerebral aqueduct is ascribed). Note the placement of a background ROI surrounding the aqueduct. This corrects for midbrain movement during the cardiac cycle.

For ease of use and continuity purposes, a curve reflecting average flow rate in mL per minute for each cardiac phase was generated. The peak diastolic flow rate (pDfr) and peak systolic flow rate (pSfr) are determined from the peak and trough of this curve.[22,25] Examples are featured in Figures 3 and 4.

Flow dynamics have proven utility in diagnosing NPH. Luetmer et al[26] reported that "CSF flow of greater than 18 mL/min suggests NPH". They have also been useful in predicting shunt response. Bradley et al[23] reported that a stroke volume greater than 42 μL correlated well with shunt response while Parkkola et al[25] reported similar outcomes with a flow rate over 10 mL per minute.

However, the postoperative drop in the above parameters was never reported with the same consistency.[25] This suggests that FR elevation, as with EI, may be symptomatic rather than causative of NPH.

(B) Diffusion Weighted Imaging (DWI)

Periventricular hyperintensity in hydrocephalus was first studied as a marker of the severity of the condition.[27] Of

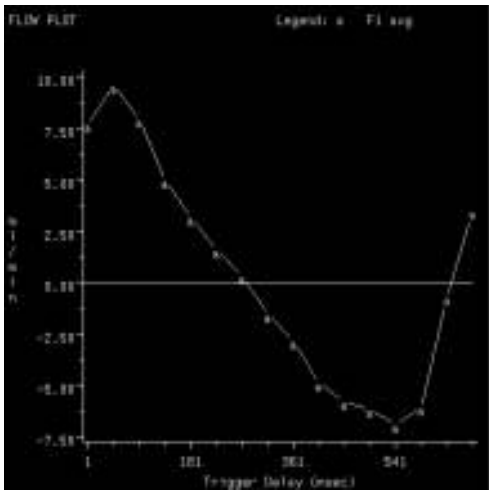

Fig. 3. Quantitative analysis demonstrating normal flow in a healthy volunteer.

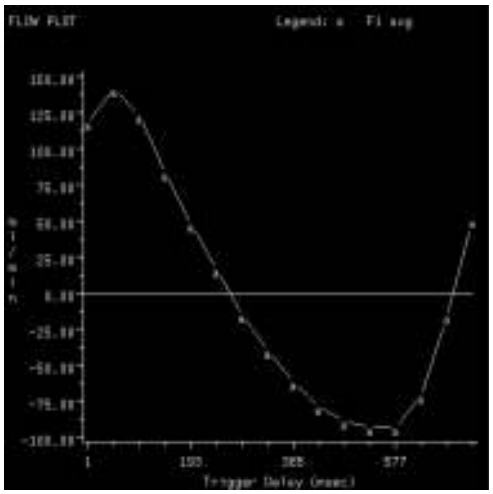

Fig. 4. Quantitative analysis demonstrating marked hyperdynamic flow rates in a NPH patient.

late, investigators have been applying DWI to evaluate both non-communicating[28] as well as communicating hydrocephalus.[29] In addition to the short acquisition time of DWI, there is capability for quantification of brain diffusibility and indirectly water content via computation of apparent diffusion coefficient (ADC) within a region of interest. Corkill et al[29] explored the viability of ADC in predicting shunt response in NPH. In their study, non-shunt responders correlated to elevated white matter ADCs, despite these same areas appearing normal on conventional MRI. The group attributed this finding to irreversible brain damage.

Bradley et al[6] used DWI to investigate the possibility of NPH being a "two hit" disease. They performed ADC mapping of 2 groups of patients with ventriculomegaly, one group symptomatic of NPH and another asymptomatic (ventriculomegaly detected incidentally). These ADCs were then compared to age-matched controls. There was a positive correlation between the ADC, the symptomatology of NPH and the extent of deep white matter changes. They determined a threshold ADC which separated between the symptomatic and asymptomatic groups. This led them to propose a 2-hit (benign external hydrocephalus in infancy, followed by deep white matter ischaemia in late adulthood) basis for NPH.

To compute the ADC of the periventricular region, a DWI sequence is applied over the entire brain. Typical parameters are TR/TE = 10/0.125 sec, FOV = 34 cm, matrix =128 x 128 matrix, slice thickness = 5 mm, b = 1000 s/mm^2. ADC is computed by placing a 45 mm^2 circular region of interest (ROI) in the periventricular region adjacent to the tip of the frontal and occipital horns of each lateral ventricle. The average of these 4 readings is then computed based on the methodology of Chun et al.[30] ADC is deemed elevated if the reading is 7.56 x 10^{-4} mm^2/s or greater.[28,30]

NPH Imaging in Singapore

Initial studies locally attested to the robustness of PC-MRI in measuring aqueductal FR and defining flow behaviour within the shunt.[24,31] A subsequent effort collecting MRI and clinical data was conducted on a national level.[32]

1. MRI Markers for Diagnosis of NPH

Thirty-five patients were initially recruited into this study. All fulfilled the initial selection criteria of NPH (at least 2 of the 3 classic symptoms of NPH, together with an elevated EI). All patients expressed an interest in surgical shunt placement and proceeded for MR imaging. Twenty-six of these met the criteria for positive response to shunting. Of these 26, only 16 were eventually shunted. Of these, only 9 returned for post-shunt MR imaging.

To arrive at these diagnostic MRI biomarkers, the data of these 9 (clinically diagnosed) cases (of NPH) was benchmarked against their age- and gender-matched controls. This is reflected in Table 1, which shows statistical significance (P <0.05) for EI, pDfr and ADC and near statistical significance for pSfr (P = 0.075).

For patients presenting with signs and symptoms of NPH, at least 2 readings on MRI greater than 0.3, 10 mL/min, -9.0 mL/min and 10.65 x 10^{-4} mm^2/s for EI, pDfr, pSfr and ADC, respectively, increase the strength of a diagnosis of NPH.

2. Clinical Evaluation of NPH

The 3 primary symptoms of NPH (i.e. gait disturbance, urinary incontinence and cognitive impairment) were assessed by 2 doctors (SN and TKK) using the scale developed by Krauss et al[33] (Table 2). The scoring format was easily understood by patients and caregivers. It was

Table 1. Comparison of Pre-operative MRI Biomarkers between Patients and Controls.

	EI	pDfr (mL/min)	pSfr (mL/min)	ADC (x 10-4 mm²/s)
Patients (n = 9)	0.33 ± 0.03	25.1 ± 10.4	-14.4 ± 11.0	12.37 ± 2.2
Controls (n = 9)	0.27 ± 0.02	7.2 ± 1.7	-6.3 ± 1.7	8.75 ± 0.99
P values	0.012	0.008	0.075	0.011

ADC: apparent diffusion coefficient; EI: Evan's Index; pDfr: peak diastolic flow rate; pSfr: peak systolic flow rate

Data are mean ± standard deviation

also easily reproducible and amenable to post-shunt scoring. Score assignment was based on the clinical examination as well as interviews with the patient and the primary caregiver.

In their paper, the authors then computed a total improvement index (TII), based on a different set of pre- and post-shunt observations.[33] Ng et al[32] elected to compute a modified total improvement index (mTII), by computing pre- and postoperative changes based on Table 2. The mTII, in essence, reflects the ratio of interval improvement over the severity of the original symptoms. As such, the ratio of improvement would range from greater than zero to a maximum of 1.0, the latter representing total improvement. On the other hand, zero would represent absence of any improvement, while a negative mTII would imply post-shunt clinical deterioration.

3. MRI Markers for Diagnosis of Shunt Response

Based on the mTII, the group of 9 patients was separated into shunt responders and non-responders. The pre- and post-shunt differences in EI, FR and ADC of these 2 distinct groups were compared. The findings are summarised in Table 3.

Responders showed a statistically significant decrease in ADC compared to non-responders even after adjusting for age and gender ($P = 0.032$). All 6 responders showed interval decrease compared to all the non-responders having an elevation in ADC.

Comparing the other 2 pre- and post-shunt measurements between groups, EI posted a drop in all 6 (100%) responders and 2 of 3 (67%) non-responders. FR (i.e. both pDfr and pSfr) showed a decrease in 4 of 6 (67%) responders and 1 of 3 (33%) non-responders. These differences were not statistically significant. Comparing against groups, both responders as well as non-responders posted cumulative decrease in FR. This observation suggests that an interval decrease in postoperative FR would not reverse the symptoms of NPH, unless the ADC posted an interval increase.

The post-shunt ADC changes (interval decrease in all responders, interval increase in all non-responders) lead us to suspect an accumulation of fluid intracranially (be it intra and/or extracellular) as the major cause of the patient's symptoms. There are many causes for elevated ADC, chief of which is related to gliosis. All changes other than water retention are permanent and would not be expected to reverse on shunting. That quantifiable interval changes are documented in all patients supports our impression of a dynamic and potentially reversible environment in the cellular spaces.

Conclusion

Work is still in progress to establish a relationship between the degree of clinical change (both improvement and deterioration) and the percentage of ADC change [Chan YH (2008) – Personal communication, National University of Singapore, Singapore]. If indeed a correlation exists, the ADC can be used as a marker for shunt response as well as shunt failure, should there be a trend reversal on follow-up.

The frontier after this is that of non-NPH dementias. Is the latter related to water accumulation? If a correlation exists, targeted therapy for reversal of this phenomenon may elicit similar reversal of dementia.

Other reported uses of CSF flow dynamics which are yet to be explored locally, include applications to reverse treatment-resistant late-life depression from microvascular angiopathy. Using phase contrast MRI, Naish et al[34] reported statistically significant CSF flow differences when comparing treatment-resistant late-life depression cases with age-matched controls. The cause may be attributed to reduced vascular compliance.[35]

Another potential of CSF flow dynamics lies in its

Table 2. Severity Grading of NPH Symptoms[33]

Grade	Gait disturbance	Urinary incontinence	Cognitive impairment
0	Normal	Normal	Normal
1	Cautious gait or impaired tandem gait	Sporadic incontinence or urge phenomenon	Minimal attentional or memory deficits
2	Considerable unstable gait	Frequent incontinence	Considerable deficits, but oriented to situative context
3	Unaided gait not possible	No or only minimal control	Not or only marginally oriented

Table 3. Comparison of MRI Biomarkers (expressed as percentage change) Pre- and Post-shunt, between Responders and Non-responders.

	Percentage change in			
	EI	**pDfr (mL/min)**	**pSfr (mL/min)**	**ADC (x 10^{-4} mm^2/s)**
Responders (n = 6)	-5.4 ± 2.2	-6.76 ± 77.4	-23.34 ± 116.6	-7.2 ± 5.0
Non-responders (n = 3)	-7.8 ± 19.6	-14.01 ± 26.1	-26.51 ± 36.13	7.7 ± 4.0
Unadjusted *P* values	0.548	0.714	0.905	0.024
P values*	0.0807	0.869	0.899	0.032

ADC: apparent diffusion coefficient; EI: Evan's Index; pDfr: peak diastolic flow rate; pSfr: peak systolic flow rate

* adjusting for age and gender

relationship to ICP. The basic model takes inspiration from the Monro-Kellie doctrine.[36,37] Several authors have attested to the utility of FR in computing ICP.[38,39]

If indeed ICP can be computed from the FR, MRI could potentially replace invasive (intracranial electrode) monitoring ICP. There is also potential in using ICP as a marker for intracranial wellness. Work is underway locally, towards an intracranial MRI examination probing ICP, vascular compliance, perfusion and water retention as surrogates for intracranial health [Ng SES (2006) – Personal communication, Medi-Rad Associates, Singapore, Singapore].

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