Clinico-Radiological Predictors of Response to CSF Diversion and Supplemental Tests in the Diagnosis of iNPH

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Abstract

Background: There is a substantial and growing body of evidence supporting the effectiveness of permanent CSF diversion in patients with ventriculomegaly who present with the classical triad of normal pressure hydrocephalus. However, not all patients fitting this definition of 'suspected iNPH' will improve with treatment. A complete understanding of the clinical and radiological predictors of shunt response in iNPH is lacking, and in particular, the usefulness of the radiological biomarker of "Disproportionate Enlargement of the Subarachnoid Space Hydrocephalus (DESH)" is controversial. Furthermore, the diagnostic accuracy of the two tests most frequently employed to identify likely shunt responders is the subject of considerable debate in the literature.

Object: To describe the efficacy and complication profile of shunt insertion in the population of patients shunted for iNPH at our institution, determine the clinico-radiological predictors of response to shunt insertion and define the usefulness of the two common tests used to select patients for intervention (CSF infusion studies and extended lumbar drainage).

Methods: Clinical data was collected retrospectively from consecutive patients referred to the hydrocephalus clinic at our institution who were deemed to have suspected idiopathic normal pressure hydrocephalus. The referral CT or MRI scan was subjected to blinded review by a Consultant Neuro-Radiologist. Data relating to gait and cognitive performance at baseline, pre- & post-ELD and at 12 months post-shunt insertion were collected to permit evaluation of CSF infusion studies and ELD as diagnostic tests.

Results: Among the 741 patients referred in the time period in question, 515 were deemed to have suspected iNPH following initial assessment, and complete baseline and outcome data were available, together with referral imaging, in 386 patients. CSF diversion was a highly effective treatment in this population with 74% of patients improved in terms of a composite outcome of gait or cognitive improvement at 12 months. Of the supplementary tests examined, only improvement in gait score during extended lumbar drainage was predictive of improvement at 12 months (coefficient 0.7, $p<0.01$), however, this performed poorly as a diagnostic test of overall improvement with a positive predictive value of 79.9% and negative predictive value of 34.4%. The overall safety of ELD was excellent with only 0.5% suffering serious complications. In terms of clinical variables predictive of improvement at 12 months, presence of urinary incontinence as a presenting feature was associated with an odds ratio of 2.2, and in terms of radiological variables, convexity tightness (odds ratio 2.4) and callosal angle (odds ratio 1.2) were predictive. Notably, DESH features did not predict improvement. In terms of the complication profile of shunt surgery, 1.6% of patients had an adverse event which required return to theatre or a prolonged inpatient stay during their index admission,

12.2% developed a chronic subdural haematoma with 3.3% of all patients requiring surgical intervention. 5.5% of shunted patients underwent shunt revision.

Conclusions: Shunt insertion was highly effective in improving gait and cognitive performance in patients with suspected iNPH in our cohort. The maximal effect of CSF diversion was achieved at 3 months and was largely maintained at 12 months post-shunt insertion. Urinary incontinence at presentation was the only clinical variable to predict shunt response. In terms of radiological metrics, only convexity tightness and callosal angle were predictive. Together these variables had a higher area under the ROC curve than either of the supplementary tests currently in use to select patients for surgical intervention. Of note, the presence of DESH did not predict improvement with CSF diversion. Further quantitative studies of the morphology of the ventricular system and distribution of CSF in iNPH may improve our ability to predict shunt response, allowing us to avoid unnecessary invasive testing and improve detection of the condition in the wider population.

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a progressive neurological disorder, characterised by unsteadiness and slowness of gait, cognitive decline and urinary urgency and incontinence that was first described by Salomon Hakim in 1964[1]. No single, unifying pathological mechanism has been found to account for the dilation of the ventricular system under seemingly normal pressure, however, there is clear and growing evidence that CSF diversion is an effective treatment. Most neurosurgeons regard clinical and radiological assessment alone to be insufficient to select patients with ventriculomegaly who will respond to shunting, leading to the use of various supplemental tests, some of which are still in use (such as extended lumbar drainage and CSF infusion studies). Others, such as radionucleotide cisternography, have fallen out of practice due to evidence that they perform poorly as a diagnostic tests. A recent population-based study of the prevalence of iNPH in Sweden[2] hinted at a high burden of undiagnosed disease in the UK, but unfortunately, in the absence of clear diagnostic parameters for shunt-responsive iNPH or an effective test for the condition, there is reluctance to commit patients to shunting (in part due to concerns about the perceived risks of the procedure).

A series of radiological signs, collectively referred to as 'Disproportionately Enlarged Subarachnoid Spaces Hydrocephalus' or 'DESH', have been proposed to differentiate iNPH from cerebral atrophy due to other dementing processes and hence predict response to shunt insertion[3], although the sample size was small and the selection method was unclear. There was initial support for the predictive value of DESH in a cohort of 108 patients, suggesting its presence conferred an odds ratio of 2.8 for shunt response[4]. However, more recent cohorts with larger sample sizes have failed to show a difference in the likelihood of shunt response between DESH and non-DESH patients[5,6]. Other researchers believe that even if DESH itself does not define a subset of patients with a higher likelihood of response to shunt insertion, other radiological markers of a supra-Sylvian obstruction to CSF flow such as an acute callosal angle, tight convexity or dilated Sylvian fissures are predictive of good outcome with a shunt.

In addition to radiological signs, many units rely on a trial of CSF drainage (with gait and cognitive assessment pre and post) in order to identify patients who are likely to respond to a shunt. The extent of drainage varies, but standard practice is drainage of >400ml of CSF over a 2-day period via a lumbar drain (or Ommaya reservoir if present), a process known as 'extended lumbar drainage' or 'ELD'. Recent evidence suggests that this test may be an effective 'rule in' with a high positive predictive value, but not an effective 'rule out' owing to its low NPV[7]. Prior to the Dutch NPH study, it was also common practice to rely upon lumbar CSF infusion studies to determine the resistance to outflow of CSF (R_{OUT}) and patients with an R_{OUT} of >12 were regarded as having an element of NPH which may be responsive to shunting. However, the Dutch NPH Study revealed a low negative

predictive value for this test at all thresholds of R_{OUT}, and as a result, it has fallen out of practice in most units[8].

Here, we describe the characteristics of a large cohort of patients referred for investigation of suspected iNPH, including the clinical and radiological predictors of shunt response (the latter obtained through blinded review of the referral scan by a Consultant Neuro-Radiologist), outcome after shunting and the diagnostic value of CSF infusion studies and extended lumbar drainage for shunt-responsive iNPH.

Methods

Consecutive patients presenting to the hydrocephalus clinic at our institution within the period April 2004 to October 2019 were included in the study if they met the following inclusion criteria: i) Age over 60 years, and; ii) Possible or suspected idiopathic normal pressure hydrocephalus on initial assessment in clinic (as defined by the Japanese Society of Neurosurgery guidelines[9]). Patients were excluded if they met any of the following criteria: i) Shunt in situ at time of referral; ii) Suspicion of secondary NPH (e.g. significant head injury, subarachnoid haemorrhage or intracranial infection); ii) Not shunted or did not undergo extended lumbar drainage testing; iii) Pre-operative imaging unavailable or unsuitable for analysis. Patient demographics and outcome data were obtained retrospectively from patient notes and clinical correspondence. Follow-up after shunt insertion was performed according to a standard protocol at our institution with outpatient review at 1-, 3- and 12-months post-insertion.

Improvement following shunting or ELD was defined as:-

- Recovered ability to walk 10 metres after ELD/shunt, OR;
- Improved along a postural assessment score (where 1 represented a bedbound patient, 2 chairbound, 3 able to sit with support, 4 able to sit without support, 5 able to stand with assistance, 6 able to stand without assistance, 7 able to walk, but less than 10 metres), OR;
- ≥20% improvement in Raftopoulos score, OR;
- ≥2 point improvement in MMSE.

The Raftopoulos score[10] is calculated using the following equation (where *t* is the number of seconds to complete a timed 10-metre gait test, *s* is the number of steps required and *A* is a factor denoting the need for assistance from another person [2 if assistance required and 1 if no assistance required]):-

$$\frac{1000}{s \times t \times A}$$

Radiological appearances were assessed by one of three Consultant Neuro-Radiologists, who were blinded to the clinical outcome data. The scan obtained in the referring hospital immediately prior to the date of the referral letter was imported to our PACS for review by one of the study Radiologists. There was excellent inter-rated reliability with a Cohen's kappa of 1 for DESH diagnosis across 15 scans which were independently reviewed by each of the Radiologists. Variables derived from the referral CT or MRI scan were as follows: Evans index, temporal horn diameter (perpendicular to the longest diameter on axial slice), callosal angle (measured perpendicular to the AC-PC axial plane at the level of the PC), tightness of the high convexity/parafalcine subarachnoid spaces, Sylvian fissure score (graded 0 for narrow, 1 for normal, 2 for mildly enlarged, 3 for moderately enlarged, 4 for severely enlarged), extent of cerebrovascular disease (graded 0 for none, 1 for mild, 2 for moderate and 3 for severe) and presence/absence of hippocampal atrophy. Sylvian fissure score and convexity/parafalcine tightness were used to determine if the patient was 'DESH positive'. Additionally, if the referral scan was an MRI, this was examined for potential obstructive causes such as aqueduct stenosis, pan ventriculomegaly with wide foramen of Magendie and large cisterna magna (PaVM)[11] or a depressed floor of the third ventricle, and the patient excluded if such a cause was found.

Statistical analysis

The anonymised dataset was analysed with Stata (StataCorp, Texas, USA). Univariate statistics were performed using simple linear or logistic regression. GraphPad Prism (GraphPad Software, California, USA) was used to generate scatterplots, regression lines and ROC curves. P values <0.05 were regarded as significant.

Results

Flow through the study is shown in Figure 1. During the 15-year data collection period, 741 patients were reviewed in the hydrocephalus clinic at our institution. Five hundred and fifteen were felt to have possible or suspected iNPH and met the study inclusion criteria. The referral CT or MRI scan was available in 79% (407) of these patients. These scans were reviewed by one of three Neuro-Radiologists who were blinded to outcome and planned radiological metrics collected. During this process, 5 patients were found to have an Evan's index <0.3 and were excluded. A further 16 patients were found to have a secondary cause of iNPH (either late-onset ventriculomegaly in aqueduct stenosis [LOVA] or pan ventriculomegaly with a wide foramen of Magendie and a large cisterna magna [PaVM]) and were also excluded. None of the remaining patients had a depressed floor of the third ventricle. The remaining population of 386 patients with 'pure' suspected iNPH patients (in which no cause of secondary or decompensated arrested hydrocephalus could be

identified) were used for the subsequent analysis. Their demographics, clinical features and the radiological findings are summarised in Tables 1 and 2.

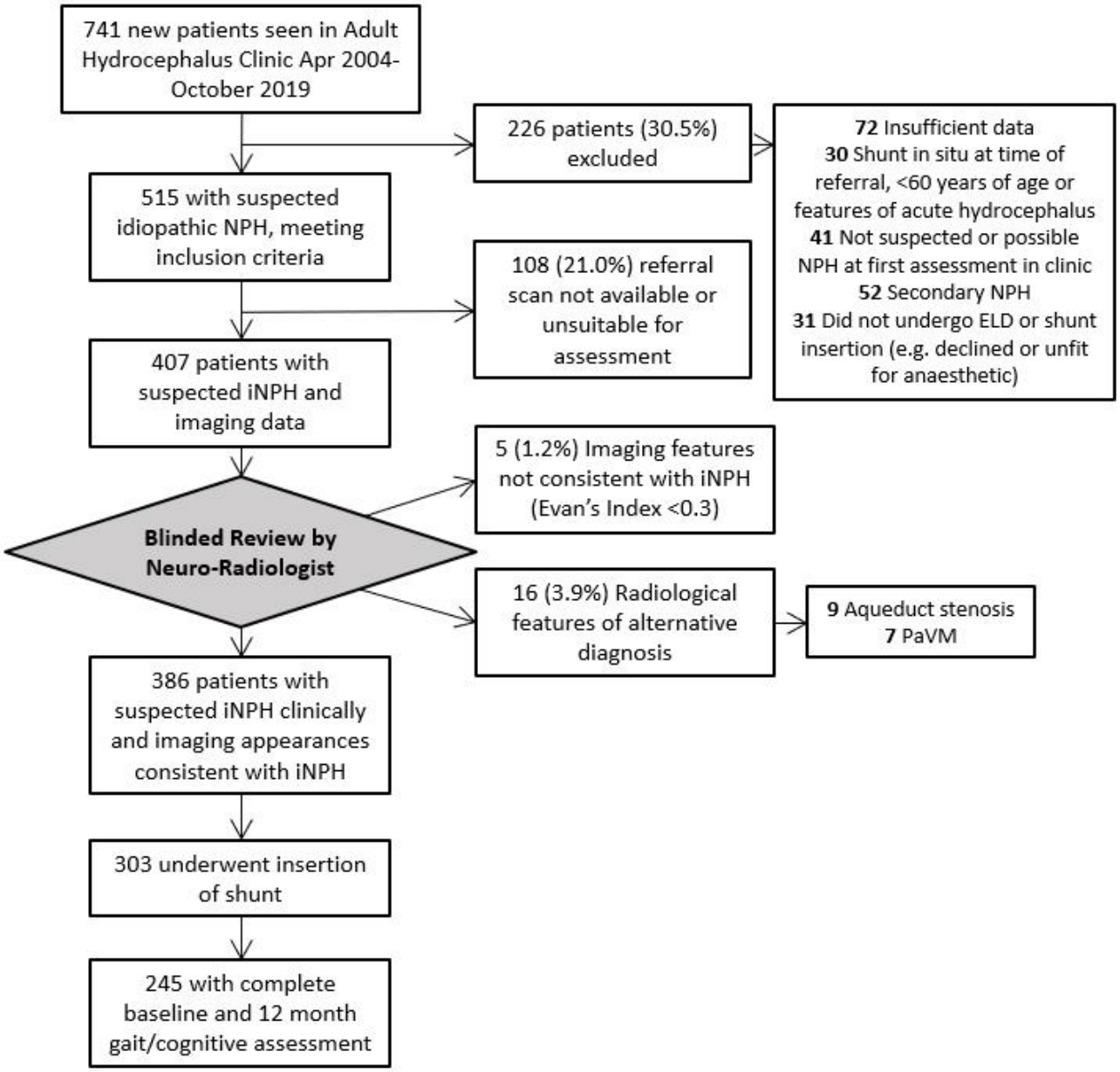

Figure 1: Flow through the study

The average age of the patients was 77.1 years and there was a preponderance of males (male-to-female ratio of 1.5). Virtually all of the patients had gait disturbance as part of their presenting symptoms (97.9%). A very high proportion (87.0%) had cognitive symptoms (usually short-term memory problems or difficulties with executive function). A lower proportion had urinary urgency or incontinence (73.0% and 65.7%, respectively). Pre-existing dementia had already been diagnosed in 8.9% of patients at referral, and the commonest co-morbid dementia was vascular.

	Mean or %	N
Demographics		
Age	77.1 years	350
Males	59.5%	385
Presenting symptoms		
Gait symptoms	97.9%	386
Duration	28.3 months	362
Cognitive symptoms	87.2%	384
Duration	17.1 months	310
Urinary urgency	71.2%	292
Duration	11.0 months	172
Urinary incontinence	66.5%	331
Duration	9.3 months	214
Dementia diagnosis prior to 1st assessment		
Any	8.6%	327
Alzheimer's Disease	3.1%	325
Frontotemporal Dementia	0.3%	325
Lewy Body Dementia	0.9%	325
Vascular Dementia	3.7%	325
Vascular risk factors		
Current or ex-smoker	50.6%	89
Diabetes	29.5%	268
Hypertension	60.3%	282
Hyperlipidaemia	15.1%	218

Table 1: Demographics and clinical features of final study population (suspected iNPH). 'N' refers to the number of patients with complete data for each variable.

	Mean [SD] or count (%) or %	N
Referral scan modality		
CT	*60.8%*	*245*
MRI	*39.2%*	*245*
Core imaging features		
Evans index	*0.39 [SD 0.04]*	*386*
Tight convexity	*66.1%*	*386*
Callosal angle	*84.2 [SD 20.0]*	*385*
Sylvian fissure score		
Decreased	*7 (1.8%)*	*386*
Normal	*99 (25.7%)*	*386*
Mildly dilated	*163 (42.2%)*	*386*
Moderately dilated	*104 (26.9%)*	*386*
Severely dilated	*13 (3.4%)*	*386*
Temporal horn diameter	*6.6 [SD 2.5]*	*245*
DESH-positive	*52.1%*	*386*
Evidence of co-morbid neurodegenerative disease		
Cerebrovascular disease score		
None	*70 (28.6%)*	*245*
Mild	*102 (41.6%)*	*245*
Moderate	*64 (26.1%)*	*245*
Severe	*9 (3.7%)*	*245*
Presence of hippocampal atrophy	*57.2%*	*383*

Table 2: Imaging data from blinded radiological assessment of referral scan for final study population (suspected iNPH). 'N' refers to the number of patients with complete data for each variable.

The mean Evans index was 0.39 (range 0.3-0.53) and the mean callosal angle was 84.2 degrees (range 46-150). Tightness of the convexity subarachnoid spaces was observed in 66.1%, and 72.5% were deemed to have dilated Sylvian fissures. Overall, 52.1% fulfilled the criteria for DESH. In terms of radiological signs of alternative dementias, 71.4% had evidence of cerebrovascular disease, and 57.2% had evidence of hippocampal atrophy.

Outcome following CSF Diversion

Three hundred and three patients underwent permanent CSF diversion. In all cases, CSF diversion consisted of a ventriculo-peritoneal shunt. All but one of these shunts had a Codman programmable valve (median initial setting 160 [range 100-200]). None of the patients underwent an ETV. Outcome following CSF diversion is shown in Figure 2. At three months follow-up, 77.7% of patients were shunt responders; at twelve months, this had decreased slightly to 73.7%.

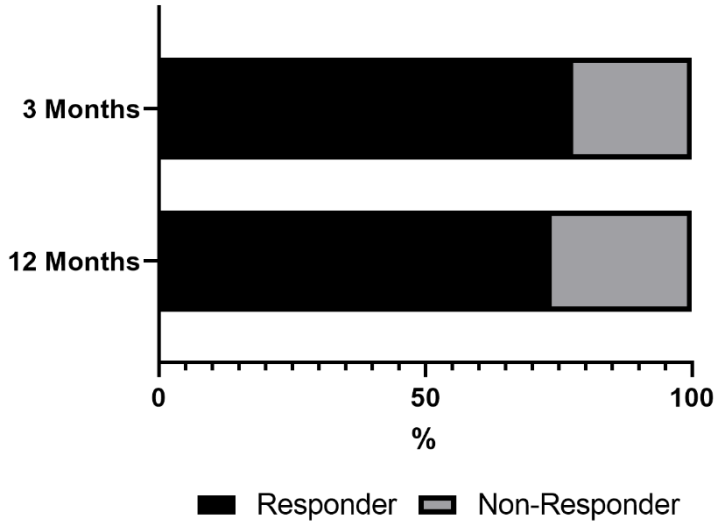

Figure 2: Proportion of patients improved (using composite outcome measure combining gait and cognitive score) at 3- and 12-months post-shunt insertion.

Change in gait score and cognitive assessment score at 3 and 12 months are shown graphically in Figure 3. Cognitive assessment with the mini-mental state examination (MMSE) improved significantly from baseline to three month follow-up (22.9 to 25.3; $p<0.01$). However, it did not increase between three and twelve months (25.3 and 25.3, respectively; $p=0.94$). Raftopoulos score also increased markedly at three months (3.3 at baseline vs. 4.3 at three months; $p<0.01$), but did not change significantly between three and twelve months (4.3 vs 4.4; $p=0.83$). This was mirrored by gait velocity, which was $0.71ms^{-1}$ at baseline, $0.84ms^{-1}$ at three months and $0.86ms^{-1}$ at twelve months.

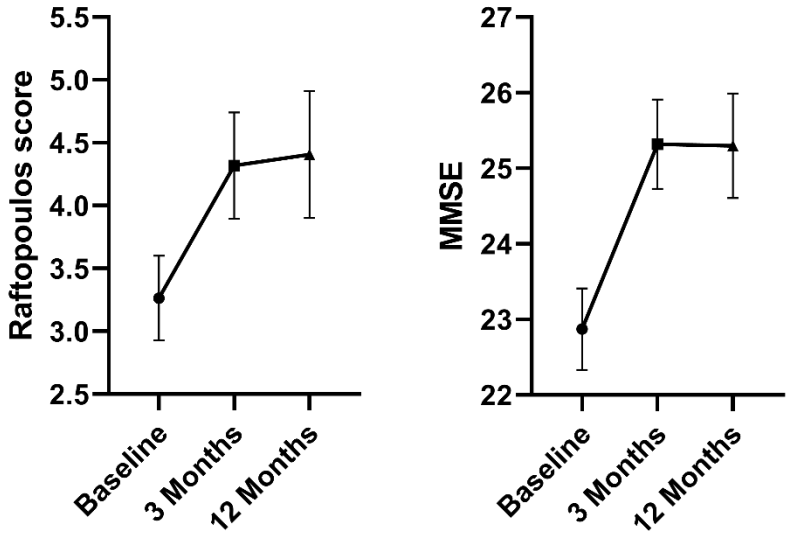

Figure 3: Absolute change in gait score and MMSE at baseline, 3- and 12-months post-shunt insertion.

Predictive value of tests of CSF dynamics

The relationships between R_{OUT} and improvement in Raftopoulos score and MMSE is shown in Figure 4 C and D, respectively. There is a very weak correlation between R_{OUT} and both change in Raftopoulos score and MMSE at 12 months (coefficients 0.06 [p=0.22] and 0.02 [p=0.78], respectively). The relationships between change in Raftopoulos score and MMSE pre- and post-extended lumbar drainage and change from baseline to 12 months are shown in Figure 4 A & B. There is a definite correlation between change in Raftopoulos score during ELD and eventual improvement at 12 months (co-efficient 0.71; $p<0.01$). Interestingly, the slope of this curve suggests that gait improvement during ELD over-estimates improvement in gait score at 12 months and suggests that some patients tend not to attain their immediate post-ELD performance at 12 months post-shunting. In contrast to the relationship between gait changes at ELD and at follow-up, no convincing relationship is seen between change in MMSE at ELD and at follow-up (co-efficient 0.21; p=0.11).

The characteristics of ELD and various thresholds of R_{OUT} as tests for shunt-responsive iNPH are shown in Table 3. All these tests had a relatively high positive predictive value (76-80%) but with a low negative predictive value (33-40.7%), therefore, all may potentially serve as a ‘rule in’ test but not as a ‘rule out’.

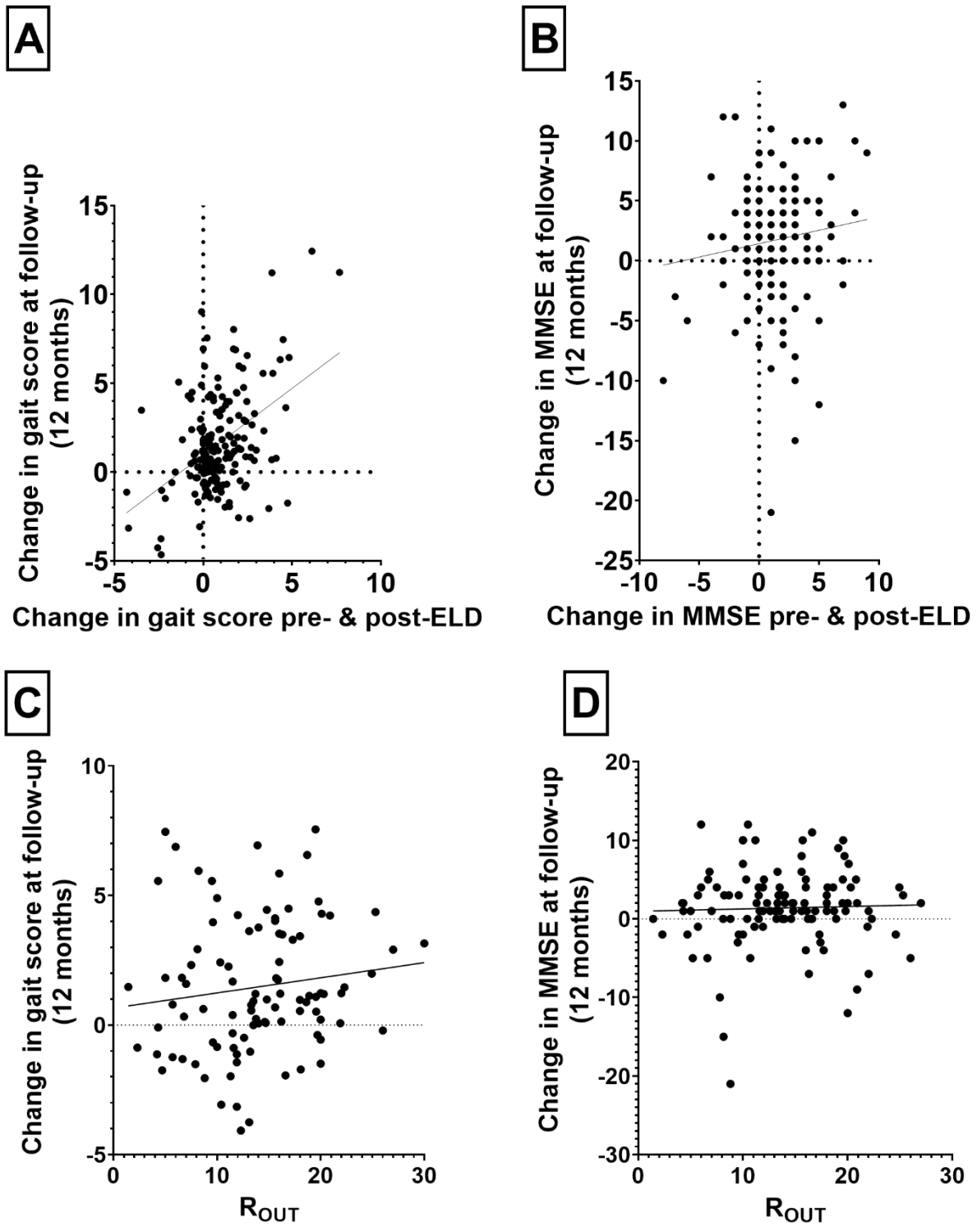

Figure 4: Scatterplots of change in gait score during ELD vs change in gait score at 12 months post-shunt insertion (A) and change in MMSE during ELD vs change in MMSE at 12 months (B) and scatterplots of R_{OUT} vs change in gait score (C) and MMSE (D) at 12 months.

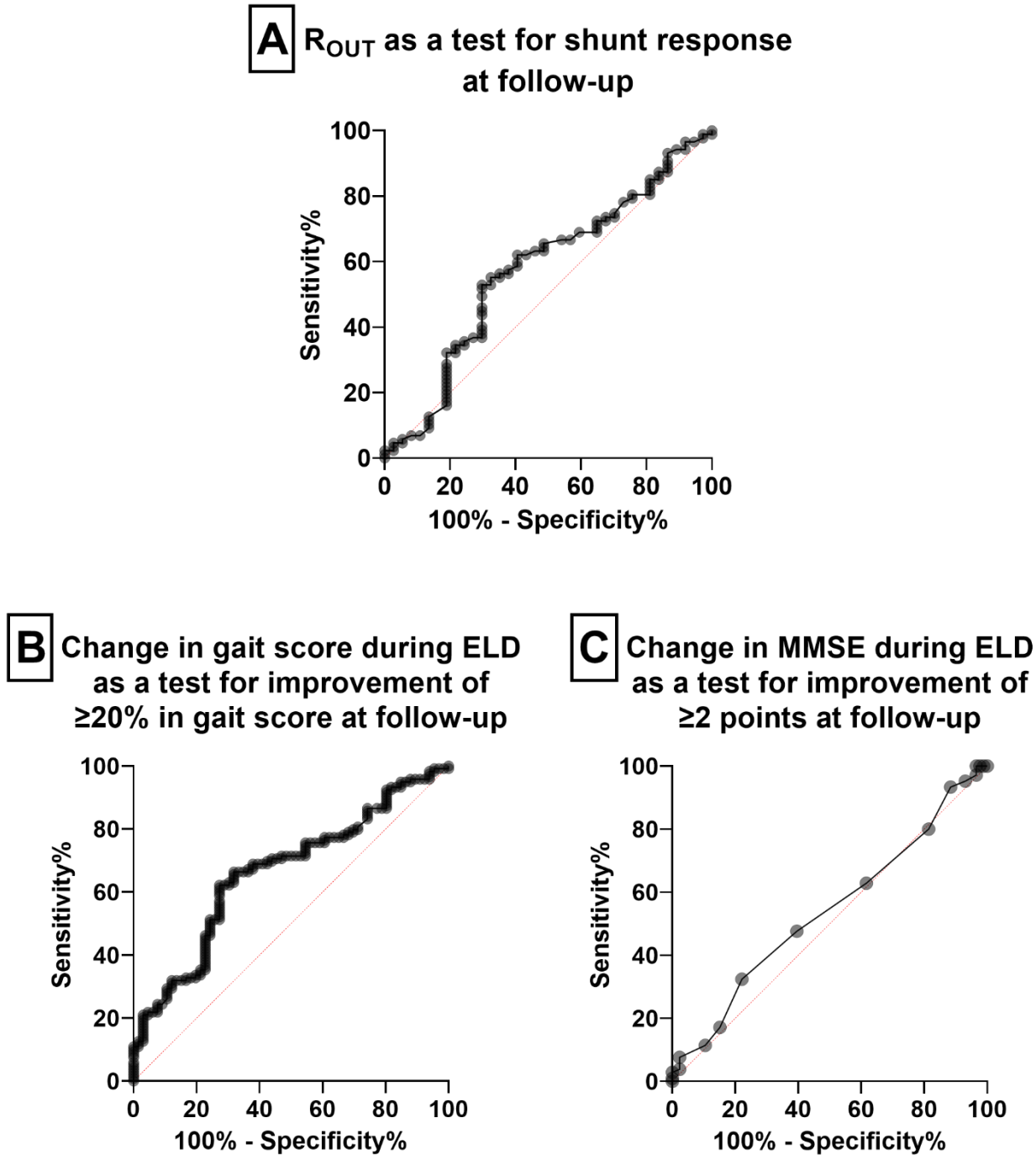

Figure 5: ROC curves for R_{OUT} as a test for improvement following shunt insertion (composite outcome measure of improvement in gait or cognitive performance) (A); change in gait score during ELD as a test of ≥20% improvement in Raftopoulos score at 12 months (B); change in MMSE as a test of improvement in MMSE of ≥2 points at 12 months follow-up (C).

Diagnostic Test	Number of patients undergoing test and subsequently shunted	Sensitivity	Specificity	PPV	NPV
ELD	234	81.4	35.5	77.8	40.7
R_{OUT}					
≥12	125	65.5	50.0	76.0	37.5
≥15	125	49.4	69.4	79.6	36.2
≥18	125	32.2	80.6	80.0	33.0

Table 3: Diagnostic test attributes of extended lumbar drainage and R_{OUT} at various cut-off thresholds.

Clinical predictors

Overall improvement at 12 months

The clinical characteristics of the shunt responders and non-responders, and their associated odds ratio for improvement post-shunting are shown in Table 4. Shunt responders tended to have a lower baseline MMSE, which is likely to be attributable to the ordinal nature of this variable, with less scope for improvement at the higher end of the scale. The two other clinical variables which predicted overall improvement at 12 months were duration of cognitive symptoms at presentation (16.8 months in responders vs. 11.5 months in non-responders [p=0.03]) and presence of urinary incontinence as a presenting feature (odds ratio 2.16, p=0.02).

Magnitude of gait and cognitive improvement at 12 months

Clinical and radiological variables and their predictive value for change in gait score are shown in Table 5. Interestingly, age is inversely related to improvement in Raftopoulos score at 12 months, i.e. older patients were less likely to improve their gait score (coefficient -0.07, p=0.03). The presence of urinary incontinence was also predictive of improvement in gait score following shunting. The two clinical variables which predicted magnitude of cognitive improvement at 12 months were baseline MMSE (as described above, possibly as a result of the reduced likelihood of improvement as patients approach 30/30) and pre-existing formal dementia diagnosis, which lessened the chance of improvement.

	N	Shunt Responders	Shunt Non-Responders	Odds Ratio	P-value
Age (years)	208	76.7	75.5	1.04	0.19
Males (%)	246	55.5	62.5	0.75	0.33
Baseline gait/cognitive assessment					
Baseline Raftopoulos Score	213	2.83	3.70	0.91	0.06
Baseline MMSE	238	22.7	25.0	0.89	<0.01
Presenting symptoms					
Gait (%)	246	98.9	100.0		0.40
Duration	235	27.8 months	28.0 months		0.96
Cognitive (%)	245	85.6	84.4	1.10	0.81
Duration	194	16.8 months	11.5 months		0.03
Urinary					
Any (%)	206	83.3	76.8	1.51	0.28
Urgency (%)	183	75.8	70.6	1.30	0.47
Duration	109	11.9 months	12.8 months		0.81
Incontinence (%)	202	69.9	51.8	2.16	0.02
Duration	139	10.5 months	6.7 months		0.22
Vascular risk factors					
Any	182	72.6	68.1	1.24	0.56
Number	182	1.06	1.09	0.97	0.86
Current or ex-smoker (%)	54	43.5	62.5	0.46	0.33
Diabetes (%)	167	22.4	31.0	0.64	0.27
Hypertension (%)	172	64.3	56.5	1.38	0.35
Hyperlipidaemia (%)	139	13.2	21.2	0.57	0.27
Dementia diagnoses					
Any (%)	203	6.0	11.3	0.50	0.21
AD (%)	203	2.7	3.8	0.70	0.68
FTD (%)	203	0.0	0.0		
LBD (%)	203	0.7	1.9	0.35	0.46
VD (%)	203	2.7	5.7	0.46	0.32
Co-morbid dementia symptoms					
Word finding difficulties	11	57.1	50.0	1.33	0.82
Parasomnia	56	22.2	18.2	1.29	0.77
Daytime somnolence	15	66.7	100.0		0.114
Vivid dreams	48	11.1	8.3	1.38	0.79
Hallucinations	61	4.2	7.7	0.52	0.61
Anosmia	47	8.1	0.0		0.35
Personality change	44	29.4	40.0	0.63	0.53
Loss of interest in activities	67	56.9	43.8	1.69	0.36
Swallowing or feeding difficulties	65	8.0	26.7	0.24	0.07

Table 4: Clinical features in shunt responders vs. non-responders (at 12 months) and their associated predictive value for shunt response.

	Change in gait score (12 months vs. baseline)		Change in MMSE (12 months vs. baseline)	
	Coefficient	**P value**	**Coefficient**	**P value**
Age (years)	-0.07	0.033	0.04	0.464
Males (%)	0.45	0.246	-0.50	0.431
Baseline gait/cognitive assessment				
Baseline Raftopoulos Score	-0.04	0.568		
Baseline MMSE			-0.36	<0.001
Presenting symptoms				
Gait (%)	0.12	0.952	2.84	0.401
Cognitive (%)	-0.72	0.171	0.17	0.852
Urinary				
Any (%)	0.82	0.129	0.23	0.784
Urgency (%)	0.43	0.404	0.37	0.576
Incontinence (%)	1.48	0.001	0.01	0.983
Vascular risk factors				
Any	0.19	0.714	0.71	0.317
Number	0.18	0.484	-0.06	0.860
Current or ex-smoker (%)	1.06	0.204	1.01	0.454
Diabetes (%)	-0.57	0.305	-0.24	0.739
Hypertension (%)	0.50	0.318	0.53	0.393
Hyperlipidaemia (%)	0.59	0.437	-1.03	0.289
Dementia diagnoses				
Any (%)	-0.36	0.671	-3.55	0.006
AD (%)	-1.15	0.375	-1.60	0.483
FTD (%)				
LBD (%)	-1.45	0.474	-3.10	0.334
VD (%)	0.91	0.484	-4.52	0.009
Co-morbid dementia symptoms				
Word finding difficulties	1.13	0.730	2.58	0.125
Parasomnia	-1.14	0.217	-0.19	0.894
Daytime somnolence	-5.10	0.024	-1.89	0.364
Vivid dreams	-0.84	0.561	1.11	0.590
Hallucinations	1.98	0.399	1.85	0.557
Anosmia	-0.67	0.743	0.54	0.820
Personality change	-1.41	0.208	-2.03	0.176
Loss of interest in activities	0.88	0.278	0.82	0.432
Swallowing or feeding difficulties	-1.67	0.190	-1.59	0.318

Table 5: Clinical variables and their associated predictive value for magnitude of gait or cognitive improvement at 12 months post-shunt insertion.

Radiological predictors

Overall improvement at 12 months

Among the radiological markers, only callosal angle and convexity tightness reached statistical significance with the composite outcome variable of regaining or improving mobility or increasing MMSE by ≥2 points (see Table 6). The presence of convexity tightness was associated with an odds ratio of 2.4 for improvement at 12 months post-shunting and a 10° decrease in callosal angle with an odds ratio of 1.17 (the more acute the callosal angle, the more likely improvement with shunting). Notably, the presence of the full complement of DESH did not predict improvement (odds ratio 1.4, p=0.26). These data are shown graphically in a forest plot in Figure 6.

	N	Shunt Responders	Shunt Non-Responders	Odds Ratio	P-value	95% CI (Lower)	95% CI (Upper)
Evans index	249	0.38	0.39	0.22	0.657	0.000	163.565
Temporal horn diameter	132	6.6mm	6.2mm	1.08	0.394	0.906	1.286
Callosal angle	248	82.7°	89.2°	1.17†	0.029	1.016	1.339
Tight convexity	249	72.7%	53.0%	2.36	0.004	1.316	4.219
Sylvian fissure score							
As continuous variable (median)	249	2	2	1.13	0.482	0.806	1.580
0 (decreased)	249	1.6%	1.5%	1.08	0.945	0.111	10.601
2-4 (mildly/moderately/ severely enlarged)	249	71.6%	74.2%	0.87	0.679	0.462	1.655
Cerebrovascular disease							
CV disease score (as continuous variable; median)	132	1	1	1.05	0.821	0.666	1.670
Presence	132	67.0%	71.9%	0.79	0.607	0.331	1.908
Hippocampal atrophy	248	60.7%	58.5%	1.10	0.756	0.616	1.948
DESH-positive	249	53.6%	45.5%	1.38	0.260	0.786	2.434

Table 6: Imaging features in shunt responders vs. non-responders (at 12 months) and their associated predictive value for shunt response. † For 10° decrease.

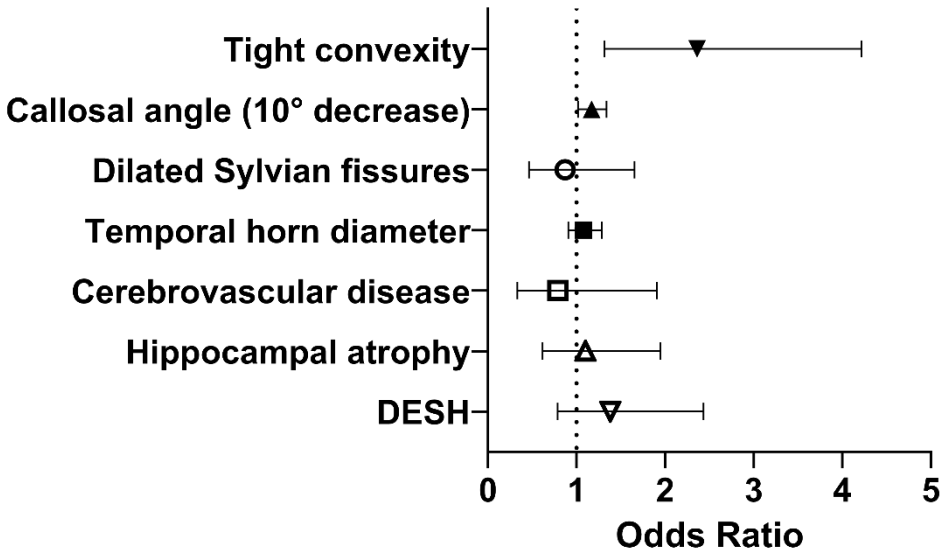

Figure 6: Odds ratio for improvement with shunting (composite outcome measure of gait or cognitive improvement at 12 months) associated with various radiological findings.

Magnitude of gait and cognitive improvement at 12 months

These results are shown in Table 7. Callosal angle reliably predicted the magnitude of both gait and cognitive improvement at 12 months (p=0.02 and p<0.01, respectively). Convexity tightness predicted the extent of improvement in MMSE at 12 months but not improvement in gait score. Surprisingly, the presence of dilated Sylvian fissures was inversely related to improvement in MMSE, suggesting that patients with dilated Sylvian fissures are less likely to improve cognitively, perhaps suggesting that dilated Sylvian fissures is more frequently a sign of cerebral atrophy than NPH.

	Change in gait score (12 months vs. baseline)		**Change in MMSE (12 months vs. baseline)**	
	Coefficient	**P value**	**Coefficient**	**P value**
Evans index	4.15	0.38	8.23	0.28
Temporal horn diameter	<0.01	0.98	0.33	0.06
Callosal angle	-0.02	0.02	-0.05	<0.01
Tight convexity	0.66	0.11	1.54	0.02
Sylvian fissure score				
As continuous variable	0.21	0.34	-0.60	0.11
0 (decreased)	-2.45	0.12	3.50	0.15
2-4 (mildly/moderately/severely enlarged)	0.10	0.81	-1.41	0.046
Cerebrovascular disease				
CV disease score	0.19	0.55	-0.22	0.644
Hippocampal atrophy	-0.11	0.79	0.39	0.541
DESH-positive	0.61	0.11	0.14	0.827

Table 7: Imaging variables and their associated predictive value for magnitude of gait or cognitive outcome at 12 months post-shunt insertion (simple linear regression).

Complications of ELD and shunt insertion

The overall complication profile of extended lumbar drainage was low (shown in Table 8). Serious complications (meningitis, nerve root injury or epidural haematoma) occurred in only 3 of the 571 patients who underwent this investigation.

	N	Prevalence
Headache requiring treatment	571	6.5%
Vomiting	571	2.6%
Blockage or displacement	571	2.3%
Sciatica	571	0.4%
Meningitis	571	0.2%
Nerve root injury	571	0.2%
Epidural haematoma	571	0.2%
Subdural haematoma	571	0.0%

Table 8: Complications from extended lumbar drainage.

The complication profile of shunt insertion is shown in Table 9. Symptoms of over-drainage symptoms (requiring downward adjustment of the shunt valve) was the most common adverse event (at 12.4%). Chronic subdural haematoma (CSDH) was also relatively common at 12.2%, however, a significantly lower proportion required surgical evacuation (3.3%), with most responding to an upward adjustment of the shunt valve setting. The median setting at which CSDH occurred was 130. Abdominal pain, which is perhaps a less-known complication of VP shunt insertion, was reported in 4.4% of cases. Blockage or malfunction occurred in 3.3% of patients (at a mean time of 2.76 years from the date of shunt insertion). Overall, 5.5% of patients required shunt revision. A new seizure disorder arose in 1.4% of patients. The remaining complications had a prevalence of <1%.

Concurrent antiplatelet agent use increased the chance of CSDH formation with an odds ratio of 2.5 ($P<0.01$; see Figure 7). A higher rate of evacuation of CSDH was also seen in the group taking an antiplatelet agent but this was not statistically significant (odds ratio 2.4, $P=0.11$). However, evacuation of CSDH only occurred in 16 of the 492 patients who underwent shunt insertion, so it is likely that the study is not adequately powered to detect a difference in this small population. No statistically significant effect of anticoagulants on CSDH rate was seen (odds ratio 2.1, $P=0.13$).

	N	Prevalence
Overdrainage symptoms	492	12.4%
Chronic subdural haematoma		
All	492	12.2%
Requiring surgical evacuation	492	3.3%
Valve setting prior (median)	492	135
Shunt revision	492	5.5%
Abdominal pain	492	4.1%
Blockage or malfunction	492	3.3%
Mean time to blockage or malfunction		2.76 years
New seizure disorder	492	1.4%
Haemorrhage (on day 1 post-operative CT scan)	492	0.8%
Malposition of proximal catheter (on day 1 post-operative CT scan)	492	0.6%
Infection	492	0.6%
Bowel injury	492	0.2%
Proximal catheter migration	492	0.2%

Table 9: Complications from shunt insertion.

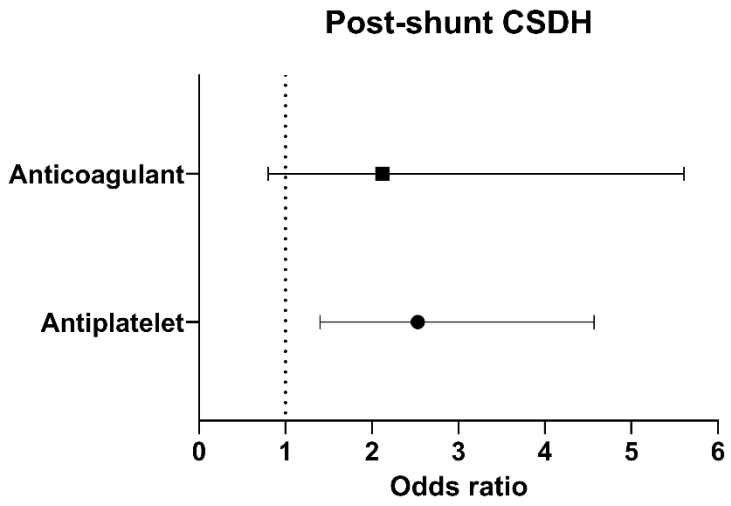

Figure 7: Odds ratio of CSDH formation associated with antiplatelet and anticoagulant drugs.

Discussion

The primary aim of this study was to identify clinical and radiological predictors of response to CSF diversion in a population of patients with suspected iNPH, and the secondary aim was to determine the diagnostic accuracy of two common tests for iNPH, namely CSF infusion studies and extended lumbar drainage. iNPH is a debilitating yet reversible condition which causes severe impairment of mobility, balance and later cognitive and urinary function. Untreated it may deprive the patient of their ability to live independently, with the concomitant costs of residential or nursing home care, which were estimated to amount to €329 million in Europe annually[12]. Furthermore, the current caseload of iNPH patients is likely to represent merely the 'tip of the iceberg' with a population-based study in Sweden finding a prevalence of iNPH is 3.7% in the over 65 age group[2]. Based on the number of confirmed iNPH cases identified is this study, the estimated incidence of iNPH in our region would be 0.002% per year, which suggests a high burden of undiagnosed disease.

In this study, the notes of all patients referred with suspected iNPH over a 15-year period were reviewed by members of the clinical team and presenting clinical features and outcome data at 3 and 12 months were extracted. Shunt insertion was found to be a highly effective treatment for patients over 60 with a phenotype compatible with iNPH – 73.7% were improved from baseline at 12 months post-shunting. In terms of predictive clinical features, urinary incontinence at presentation was predictive of shunt response at 12 months, and there was a significantly significant difference in the duration of cognitive symptoms at presentation. It is likely that the presence of urinary incontinence serves to differentiate iNPH patients from patients with either an alternative cause of gait deterioration, such as vascular parkinsonism, and from patients with other dementing processes such as Alzheimer's or vascular dementia (where urinary incontinence is likely to emerge late in the disease process).

The presenting scans of patients with suspected iNPH were subject to blinded review by our study Neuro-Radiologists, who assessed the scans according to conventional radiological metrics of hydrocephalus and also determined if there were signs of co-morbid neuro-degenerative processes. There was high inter-rater reliability – for instance, Cohen's kappa for DESH diagnosis was 1 (representing perfect agreement for 15 scans which were independently reviewed). The two radiological variables predictive of shunt response were convexity tightness and decreasing callosal angle. Interestingly, neither Sylvian fissure score, nor DESH were predictive. In fact, in terms of change in MMSE at 12 months, the presence of dilated Sylvian fissures was actually associated with less improvement, suggesting that this is usually indicative of atrophy that an active hydrocephalic process.

In addition to clinico-radiological predictors, two common supplementary tests used in determining decision to shunt were evaluated. Neither of these tests were used as the sole determinant of this decision and were instead used as one element of a more holistic evaluation. For both ELD and CSF infusion studies, the PPV was relatively high (76-80%) but the NPV was low (33-41%) suggesting these tests should be used a 'rule in' rather than 'rule out' test. Interestingly, the area under the ROC curve for the clinico-radiological predictors included in a logistic regression model is higher than the AUC for any of the diagnostic tests evaluated. These results are very similar to those for ELD in the largest cohort study evaluating this test in rigorous fashion by shunting all patients who underwent the test (Walchenbach et al.[7]), and the diagnostic test characteristics for R_{OUT} concord very well with the results of the Dutch NPH study[8]. Although ELD performs poorly as a standalone diagnostic test, our data demonstrated a clear correlation between improvement in Raftopoulos score at ELD and that seen at 12 month post-shunting, which supports the idea that the test may be helpful in guiding patients as to the potential benefits of permanent CSF diversion in equivocal cases or in patients with high anaesthetic risks. A previous study addressing the relationship between magnitude of ELD improvement and magnitude of shunt improvement reached the same conclusion[13]. We have not assessed here the effect of introducing a post-discharge diary for patients undergoing ELD where the patient or their carers record improvements in gait, cognitive or urinary symptoms during the week following discharge – this analysis is ongoing.

Although the presence of a pre-existing dementia diagnosis lessened the degree of improvement in MMSE at 12 months, we were not able to reproduce the finding of Krauss and colleagues[14] that the presence of cerebrovascular disease is inversely related to shunt outcome in suspected iNPH, nor was there any association with the presence of hippocampal atrophy, which was demonstrated in both shunt responders and non-responders with similar frequency.

In terms of shunt complication profile, our data confirm the impression that shunt insertion is not without risks, but the incidence of complications requiring surgical intervention (evacuation of haematoma or shunt revision/removal) is lower than that reported in the current literature, which was summarised in Hebb and Cusimano in 2001[15]. The average rate of this class of complication was 22% in their pooled analysis and 8.8% in our cohort. This may represent progress in the technical aspects of shunt insertion, and to some extent, new shunt technology such as programmable valves and antibiotic-impregnated catheters.

The main limitations of this study are those inherent in any retrospective cohort – the associations demonstrated do not prove causation. Regarding the diagnostic characteristics of the supplemental tests, although neither of the tests were used as the sole determinant of the decision to shunt and many test-negative patients underwent shunting, the only completely robust way of determining these metrics is a study designed for the purpose in which all patients (regardless of test outcome)

are given the treatment (that is, shunt insertion), any other design removes true negatives and false negatives compromising the estimation of NPV. Furthermore, including subjective assessment of NPH symptoms in the week following ELD may improve the reliability of the test, particularly the NPV but reducing false negative results. Finally, regarding the effect of the radiological variables on outcome, it may be that the magnitude of effect is greatly diminished by the enrichment of a highly-selected population with a very high pre-test probability – it may be, for instance, that in the wider population, characteristics such as convexity tightness (or indeed DESH) could be associated with a substantially increased risk of iNPH but in the population enriched for a strong clinical phenotype, this effect is less prominent.

Overall, these data strongly suggest that referral imaging data can be used to enhance patient selection for surgery, given the significant effect of callosal angle and convexity tightness, however, the effects of these two variables is not sufficient to use this as a reliable test (AUC is still <0.8). In order to enhance stratification of this population, it is crucial to move away from classical radiological metrics of hydrocephalus and employ a higher throughput approach with volumetric analysis of CSF distribution and morphological analysis of the ventricular system to identify as yet undetected features of intermittently raised pressure or indeed morphological changes in the brain which suggest an alternative diagnosis. Regarding the usefulness of supplemental tests, our data suggest that using a purely objective assessment of ELD outcome, it performed poorly as a 'rule out' test, however, incorporating subjective improvement in gait/balance, 'real world' cognitive ability and urgency/incontinence may improve the reliability of the test and this analysis is in progress. It is also important to emphasise that ELD is helpful in demonstrating the potential benefits of shunting to the patient, which aids their decision making, and is a low risk procedure. It is important to note that even in the 3 of 571 patients who developed a 'serious' adverse event according to our strict definition, none sustained permanent neurological worsening as a result. ELD also serves an important function in identifying patients who are particularly sensitive to low-pressure symptoms who may benefit from a higher valve setting at the time of shunt insertion.

Conclusion

In this large cohort of consecutively referred iNPH patients, urinary incontinence at referral and longer duration of cognitive symptoms (relative to overall symptom duration) were predictive of improvement with CSF diversion at 12 months. More acute callosal angle and convexity tightness also predicted some of the variability in shunt response. Taken together, these variables do not predict shunt outcome with a high degree of accuracy and neither of the assessed supplementary tests had an acceptable accuracy profile to be wholly relied upon. Further analysis of the effect of including patient-reported subjective improvement following ELD is the subject of ongoing investigation which may reveal improvement diagnostic test characteristics. A more nuanced

analysis of the morphology of the ventricular system and distribution of CSF in iNPH may aid in identifying novel radiological signs of the condition and of shunt-responsiveness. Given the current absence of a reliable test, and the high efficacy of shunt insertion and improving safety profile (particularly with a higher opening valve pressure), there is need for a randomised controlled trial comparing shunting in patients with ventriculomegaly and gait or cognitive impairment following supplemental testing and shunting on clinical grounds.

References

1. Hakim S. Some observations on CSF pressure. Hydrocephalic syndrome in adults with “normal” CSF pressure (Recognition of a new syndrome). 1964.

2. Andersson J, Rosell M, Kockum K, et al. Prevalence of idiopathic normal pressure hydrocephalus: A prospective, population-based study. *PloS one* 2019;14:e0217705.

3. Kitagaki H, Mori E, Ishii K, et al. CSF spaces in idiopathic normal pressure hydrocephalus: morphology and volumetry. *AJNR American journal of neuroradiology* 1998;19:1277–1284.

4. Virhammar J, Laurell K, Cesarini KG, Larsson E-M. Preoperative prognostic value of MRI findings in 108 patients with idiopathic normal pressure hydrocephalus. *American Journal of Neuroradiology* 2014;35:2311–2318.

5. Ziegelitz D, Agerskov S, Wallin M, et al. Absence of disproportionately enlarged subarachnoid space hydrocephalus, a sharp callosal angle, or other morphologic MRI markers should not be used to exclude patients with idiopathic normal pressure hydrocephalus from shunt surgery. *American Journal of Neuroradiology* 2019;40:74–79.

6. Ahmed AK, Luciano M, Rigamonti D, et al. Does the presence or absence of DESH predict outcomes in adult hydrocephalus? *American Journal of Neuroradiology* 2018;39:2022–2026.

7. Walchenbach R, Geiger E, Thomeer RTWM, Vanneste JAL. The value of temporary external lumbar CSF drainage in predicting the outcome of shunting on normal pressure hydrocephalus. *Journal of neurology, neurosurgery, and psychiatry* 2002;72:503–506.

8. Boon AJ, Tans JT, Delwel EJ, et al. Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *Journal of neurosurgery* 1997;87:687–693.

9. Mori E, Ishikawa M, Kato T, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. *Neurologia medico-chirurgica* 2012;52:775–809.

10. Raftopoulos C. Hydrocéphalie idiopathique à pression normale: analyse des ondes de pression intercrânienne permettant l’évaluation de l’amélioration clinique après dérivation ; définition de l’amélioration des fonctions cognitives et signification de l’augmentation de l. 1994.

11. Kageyama H, Miyajima M, Ogino I, et al. Panventriculomegaly with a wide foramen of Magendie and large cisterna magna. *Journal of neurosurgery* 2016;124:1858–1866.

12. Martin-Laez R, Caballero-Arzapalo H, Lopez-Menendez LA, et al. Epidemiology of Idiopathic Normal Pressure Hydrocephalus: A Systematic Review of the Literature. *World neurosurgery* 2015;84:2002–2009.

13. Li Z, Naugle RI, Wood A, et al. Intermittent lumbar drainage with functional testing in the diagnosis of normal-pressure hydrocephalus. *European journal of pediatric surgery* 2001;11 Suppl 1:S38-40.

14. Krauss JK, Droste DW, Vach W, et al. Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. *Neurosurgery* 1996;39:292–300.

15. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. *Neurosurgery* 2001;49:1166.