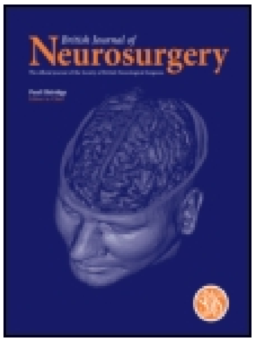

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ORIGINAL ARTICLE

Apathy, ventriculomegaly and neurocognitive improvement following shunt surgery in normal pressure hydrocephalus

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Abstract

***Introduction*. Apathy – impaired motivation and goal-directed behaviour – is a common yet often overlooked symptom in normal pressure hydrocephalus (NPH). Caudate atrophy often yields apathetic symptoms; however, this structural and functional relationship has not yet been explored in NPH. Additionally, little is known about the relationship between apathy and post-shunt cognitive recovery. *Methods*. This audit investigated whether apathetic symptoms improve following shunt surgery in NPH, and whether this relates to cognitive response. In addition, we assessed the relationship between ventriculomegaly and apathy using the bicaudate ratio. Twenty-two patients with NPH completed the Mini-Mental State Examination (MMSE), the Apathy Evaluation Scale (AES) and the Geriatric Depression Scale (GDS) before and 3–9 months after shunt surgery. Pre-operative ventriculomegaly was correlated with pre-operative AES and GDS scores. Difference scores (post-shunt minus baseline values) for AES and GDS were correlated with cognitive outcome. *Results*. Greater pre-operative ventriculomegaly was associated with increased level of apathy and depression. A reduction in apathetic symptoms following shunt surgery was associated with improved performance on the MMSE. *Conclusions*. Apathy may be indicative of a greater degree of subcortical atrophy in NPH and may relate to functional outcome.**

Keywords: apathy; audit; caudate nucleus; cognitive function; normal pressure hydrocephalus

Introduction

Normal pressure hydrocephalus (NPH) is a clinical syndrome resulting from a buildup of cerebrospinal fluid (CSF) in the brain. It is characterised by gait apraxia, cognitive decline, urinary incontinence, ventriculomegaly (ventricular enlargement) and apparently normal CSF pressure at lumbar puncture.[1] Although cognitive decline is commonly associated with NPH, the nature of NPH-related dementia is difficult to characterise. Following treatment with a ventriculoperitoneal shunt to divert CSF, cognitive function has been shown to improve.[2,3] Hence, NPH represents a reversible form of dementia.[2] Problematically, apathy is often observed in NPH patients.[2,4] This symptom may be a significant obstacle for cognition and functional outcome. Increased apathy is associated with decreased functional level across a range of disorders (e.g. Alzheimer's disease and stroke)[5] and should thus be an important consideration for NPH treatment.

It has been argued that symptoms associated with NPH may be attributed to subcortical pathology.[2] For example, the caudate nucleus, a subcortical structure and part of the fronto-subcortical dopaminergic system, plays a role in reward processing and motivation.[6] Importantly, damage to these areas has been associated with apathy.[7,8] Diminished caudate volume has been observed in patients with NPH,[2] it is therefore possible that caudate atrophy and damage to associated striatal circuitry in NPH may underlie apathetic behaviour. It is not yet established whether caudate atrophy relates to degree of ventriculomegaly. Ventriculomegaly may be assessed using the bicaudate ratio (BCR) – the width of the lateral ventricles at the level of the body of the caudate nuclei as a percentage of the width of brain across the same line (Fig. 1). BCR is a useful measure as it is easily obtainable without complex computerised techniques. This audit investigates whether BCR relates to degree of apathy in patients with NPH. In addition, cognition and apathy were assessed before and after shunt surgery to explore the relationship

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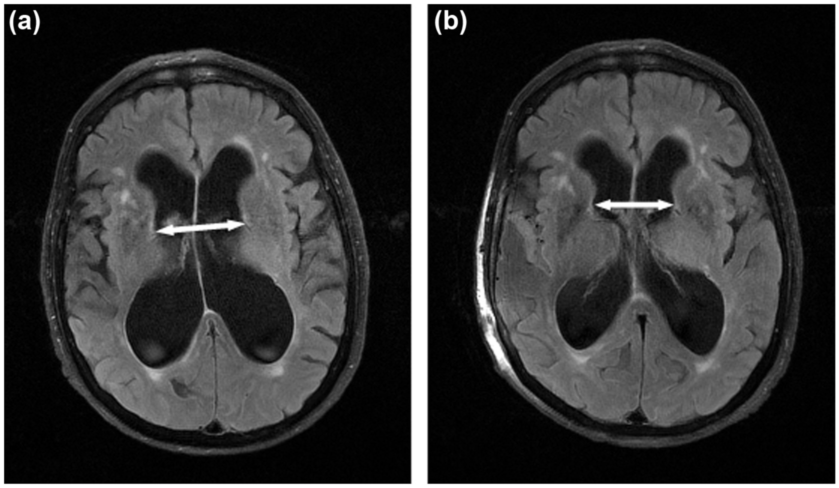

Fig. 1. Measurement of BCR on MRI axial flair. An illustration of BCR before (a) and after (b) shunt surgery. BCR is calculated as the width of the lateral ventricles at the level of the body of the caudate nuclei as a percentage of the width of brain across the same line. In this example, BCR = 0.32 at pre-shunt scan and reduces to 0.31 at 3-month post-shunt scan.

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between apathy and cognitive outcome, and to provide a clearer profile of the mechanisms driving post-shunt recovery.

Materials and methods

Patients

As part of an ongoing audit, a clinically representative sample of 22 patients with NPH was included in the present study. Patients were assessed using a brief neuropsychological test battery as part of their normal clinical pathway prior to shunt surgery and 3–9 months after surgery ($M = 4.17$ months). Patients were referred by a neurosurgeon (JDP) based on the presence of a clinical picture of NPH.[3] Neuropsychological test data were collected at the CSF clinic led by JDP, Addenbrooke's Hospital.

Imaging analysis and neuropsychological assessment

Patients were scanned using magnetic resonance imaging (MRI) or computed tomography (CT) prior to shunt surgery as part of the standard diagnostic procedure. MRI scans were used by a neurosurgeon (JDP) to calculate BCRs.[9] Where these were unavailable, CT scans were used (n = 5). Figure 1 provides an illustration of BCR before and following shunt

Table I. NPH patients demographics.

Patient No.	Age	Sex	IQ	Years of education	Time to retest (months)	Aetiology	Gait Disturb	Incontinence	MMSE Pre	MMSE Post	Pre BCR[a]
1	61	M	120	12	3	Idiopathic	+	+	23	26	0.33
2	49	M	112	n/a	4	Secondary to IV ventricular outlet obstruction	+	–	26	26	0.23[c]
3	56	M	117	11	3	Secondary to pineal tumour and radiotherapy	+	–	28	28	0.30
4	73	M	98	11	3	Idiopathic	+	+	18	24	0.27
5	74	F	100	n/a	9	Idiopathic	+	–	28	25	0.31[c]
6	60	M	116	12	3	Idiopathic	+	–	28	28	0.30
7	65	M	92	10	8	Aqueduct stenosis	+	–	n/a	29	0.37
8	83	M	116	11	5	Idiopathic	+	n/a	28	23	0.29
9	79	F	100	11	5	Idiopathic	–	–	18	21	0.29
10	74	M	87	10	2	Query aqueduct stenosis	+	n/a	18	24	0.28
11	76	M	103	11	5	Idiopathic	+	+	23	21	0.29
12	52	M	109	11	3	Aqueduct stenosis	+	–	27	29	0.29
13	62	F	100	11	2	Secondary to Chiari malformation, aqueduct stenosis	+	–	29	25	0.27
14	82	F	115	9	3	Idiopathic	+	+	26	27	0.26[c]
15	56	F	111	16	3	Idiopathic	+	n/a	21	24	0.30[c]
16	77	M	115	9	3	Idiopathic	+	n/a	27	28	0.30
17	79	F	124	12	8	Idiopathic	++[b]	n/a	26	27	0.33
18	75	M	125	14	3	Idiopathic	+	–	27	30	0.28
19	81	M	120	14	3	Idiopathic	+	–	27	28	0.26[c]
20	52	F	109	18	8	Aqueduct stenosis	+	–	24	27	0.29
21	66	M	92	12	5	Idiopathic	+	+	26	27	0.24
22	71	F	126	17	4	Idiopathic	+	–	27	26	0.26

[a]pre-operative BCR (higher BCR = greater degree of ventriculomegaly), [b]patient in a wheelchair, [c]taken from CT scans, n/a = information not available.

Table II. Neuropsychological tests results at baseline and 3–9 months post-operatively.

Neuropsychological test	N	Pre-operative Median (IQR)	Post-operative Median (IQR)	t/Z	df	p	change[c] ±
AES[a]	18	17.50 (10.5)	10.00 (9.5)	− 1.87		0.06	+
GDS[a]	21	6.00 (6)	2.00 (4.5)	− 1.29		0.20	+
Phonemic fluency*	21	27.90 ± 10.97[b]	34.14 ± 16.43[b]	− 2.38	20	0.03	+
Semantic fluency**	22	12.32 ± 5.79[b]	15.82 ± 7.02[b]	− 3.06	21	0.006	+
HVLT immediate	22	4.95 ± 1.86[b]	5.05 ± 2.14[b]	− 0.20	21	0.85	+
HVLT learning	22	17.27 ± 5.42[b]	18.91 ± 6.82[b]	− 1.26	21	0.22	+
HVLT delayed[a]*	22	1.00 (3)	3.00 (7)	− 2.14		0.03	+
HVLT recognition[a]**	22	21.00 (3)	23.00 (2)	− 3.00		0.003	+
MMSE[a]	22	26.00 (4)	26.50 (3.75)	− 1.72		0.09	+

*p< 0.05, **p < 0.01, [a]non-parametric test, [b]mean ± SD, [c]direction of change (+ = improvement, − = decline).

surgery in NPH. IQ and global function were assessed using the National Adult Reading Test (NART)[9] and the Mini-Mental State Examination (MMSE),[10] respectively. Phonemic and semantic fluency were measured using the Controlled Oral Word Association Test (COWAT).[11] Verbal memory and learning were measured using the Hopkins Verbal Learning Test (HVLT).[12] Mood was assessed by the Geriatric Depression Scale (GDS short form)[13] and/or the self-report version of the Apathy Evaluation Scale (AES).[14]

Statistical analysis

Pre-operative BCRs were correlated with patients' pre-operative AES score, and GDS score for comparison. BCR was also correlated with pre-operative MMSE score, IQ and age. Bivariate correlations were conducted using Spearman's *rho*. Pre- and post-operative neuropsychological test scores were compared using paired samples *t*-tests. One outlier was identified and removed from the phonemic fluency analysis as the pre-operative score was >2.5 standard deviations (SDs) above the mean. Scores in the AES, GDS, HVLT delayed, HVLT recognition and MMSE violated assumptions of normality; Wilcoxon signed-rank tests were therefore used to compare scores in these tests. To investigate the relationship between change in apathy (AES) and change in neuropsychological test scores, pre-operative scores were subtracted from post-operative scores to obtain a 'change' (difference) score for each test. Correlations were then conducted using Spearman's *rho*. Correlations between change in depression (GDS) and change in neuropsychological test scores were conducted for comparison.

Results

Fourteen patients were male and eight were female. Mean (SD) age in years was 68.3 (10.8). Mean IQ and years of education were 109.4 (11.38) and 12.1 (2.49), respectively. Mean baseline MMSE was 25 (3.52). Mean pre-operative BCR was 0.29 (0.03). Individual patient details are shown in Table I.

Significant positive correlations were observed between pre-operative BCR and pre-operative AES score, $r_s = 0.51$, $p = 0.03$, and between pre-operative BCR and pre-operative GDS score, $r_s = 0.52$, $p = 0.02$. These significant correlations indicate that greater pre-operative BCR (greater degree of ventriculomegaly) was associated with greater levels of apathy and depression. Although there was no significant correlation between BCR and age, partial correlations were conducted for both analyses controlling for age. Both AES score and GDS score remained significantly positively correlated with pre-operative BCR when controlling for effects of age.

There were significant within-group differences between pre-operative and post-operative scores in phonemic fluency, semantic fluency, HVLT delayed and HVLT recognition, all in the direction of improvement after shunt surgery (Table II). No other significant group differences were observed. A Wilcoxon signed-ranks test demonstrated a non-significant trend for decreased apathy (AES) post-operatively, $Z = -1.87$, $p = 0.06$. A *post-hoc* power calculation was conducted using G*Power 3 to determine an estimate of the sample size required to achieve a significant difference in AES scores before and 3–9 months after the operation. With alpha set at 0.05 and power set at 0.80, approximately 34 participants would be needed to achieve a medium effect size ($d = 0.45$).

Table III shows results of correlations between AES and GDS change scores with change scores in the remaining neuropsychological tests. A significant positive correlation was observed between AES change and GDS change, as AES score decreases so does GDS score (both improve). Additionally, there was a significant negative correlation between AES change and MMSE change. The nature of this relationship can be seen in Fig. 2. As AES score decreases, MMSE score increases. That is, a reduction in apathy is associated

Table III. Bivariate correlations between change in apathy and change in depression with change in neuropsychological test scores.

Variables	Age	IQ	Time to retest	BCR	AES change	GDS change	Phonemic fluency change	Semantic fluency change	HVLT immediate change	HVLT total change	HVLT delayed change	HVLT recognition change	MMSE change
AES change	0.05	0.21	0.28	− 0.36	–	0.51*	− 0.38	− 0.43	− 0.24	− 0.27	0.09	− 0.15	− 0.70**
GDS change	0.27	0.10	0.25	− 0.08	0.51*	–	− 0.16	− 0.30	0.03	− 0.18	− 0.05	− 0.04	− 0.41

Results represent Spearman's *rho* values.
*p< 0.05, **p < 0.01. 'Change' scores were calculated by subtracting pre-shunt scores from post-shunt scores.

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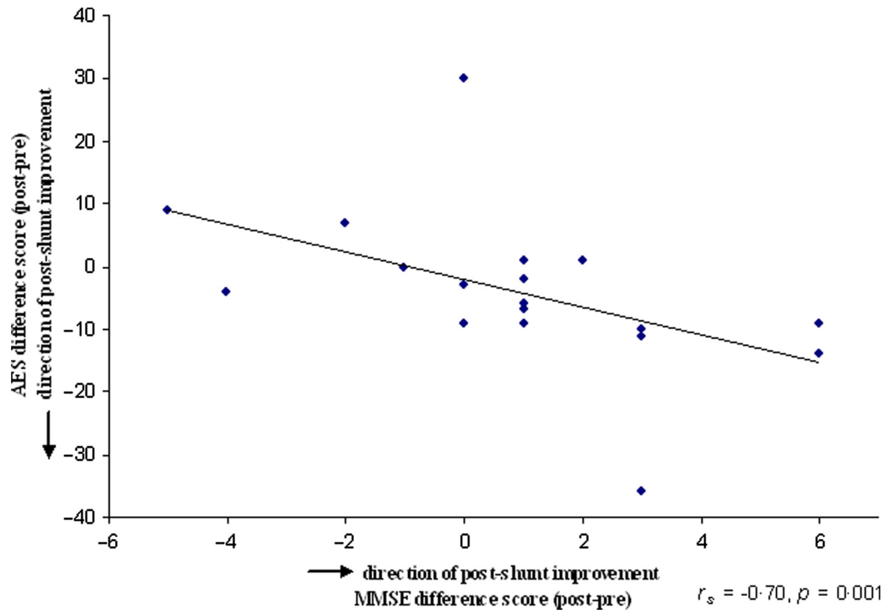

Fig. 2. Apathy and cognitive outcome. Scatterplot showing the relationship between patients' change in AES scores and change in MMSE score, $r_s = -0.70$, $p = 0.001$. Higher positive MMSE difference score indicates improvement in 'global' cognitive functioning from pre-operative to post-operative assessment, while a negative AES difference score indicates lower severity of apathy at post-operative assessment.

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with increased functional level as measured by the MMSE. No significant correlation was observed between GDS and MMSE change.

Discussion

This audit investigated whether BCR (degree of ventriculomegaly) relates to degree of apathy in patients with NPH, and the relationship between changes in cognition with change in apathy after shunt treatment. Results revealed significant improvements from baseline to follow-up in tests of phonemic and semantic fluency, delayed verbal recall and recognition memory. Additionally, pre-operative BCR was positively correlated with pre-operative degree of apathy and depression. There was a non-significant trend for improved apathy scores following shunt surgery. Importantly, we found that a reduction in apathy was associated with improved global cognition. No relationship was observed between change in global cognition and changes in depressive symptoms.

These findings highlight the importance of assessing apathy in patients with NPH. Apathy is associated with striatal dopaminergic pathology.[8] Since pre-operative BCR was positively associated with degree of apathy, the symptom of apathy may indicate greater subcortical brain atrophy, possibly leading to impaired functioning of striatal dopamine pathways in patients with NPH. Additionally, our findings suggest that alleviation of the symptom of apathy following shunt surgery is linked to improved functional level as measured by the MMSE. Keenan et al. found that administration of the psychostimulant drug: methylphenidate was associated with reduced apathetic symptoms and increased performance in a spatial recognition task in a patient with NPH.[4] Methylphenidate inhibits dopamine reuptake in the brain by blocking dopamine transporters[15,16] and it was concluded that increased dopamine level in the brain following methylphenidate administration may account for the observed reduction in apathy.[4] These findings suggest a possible dopaminergic link to apathy and the cognitive deficits observed in NPH.

BCR also positively correlated with degree of depression in our patient sample and as level of apathy reduced (improved) post-operatively so did the level of depression. However, no association was observed between change in depression level and MMSE score. Distorted reward processing, an aspect of depression,[17] likely overlaps with symptoms of apathy and therefore this aspect could improve simultaneously with reduced apathetic symptoms following shunt surgery.

Conclusions

BCR is an easily obtainable measure of degree of ventriculomegaly in patients with NPH. We observed a relationship between pre-operative BCR and degree of apathy. Additionally, our findings suggest a potential role of apathy in patients' post-shunt functional outcome, highlighting the importance of assessing this symptom in NPH (a symptom which currently is not commonly assessed). These results may also demonstrate that to some extent apathetic symptoms improve following shunt treatment. The relationship between BCR and caudate atrophy in NPH should be examined further.

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