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Predictors of cognitive impairment in pseudotumor cerebri

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ABSTRACT

Aims of the study: We aimed to define the cognitive burden of the largest pseudotumor cerebri syndrome (PTCS) population to date, compare objective to subjective cognitive dysfunction, and determine clinical predictors of cognitive dysfunction amongst an array of previously unstudied factors.

Clinical rationale: Patients with PTCS commonly report cognitive dysfunction, a factor associated with poor quality of life. It is not definitively known whether cognitive impairment is present in these patients, and what features of the syndrome predict impairment.

Materials and methods: We administered a cognitive battery consisting of the National Adult Reading Test, Mini-Mental Status Exam, Digit Span, Boston Naming Test, Rey Auditory Verbal Learning Test, Clock Drawing, Trail Making Test, Controlled Oral Word Association, and Category Fluency. Cognitive impairment was defined as mild-single domain with one test score, and mild-multiple domain with two scores, more than two standard deviations below the mean for age-, gender-, and education-adjusted norms.

Results: One-hundred and one prospectively recruited PTCS patients were enrolled. The objective testing showed 30 patients had mild-single domain impairment, and 25 had mild-multi domain impairment. More patients without objective cognitive impairment had transverse venous sinus stenosis, but otherwise the groups did not differ. Two measures of headache severity, the Headache Impact Test and pain on the Numeric Rating Scale, were negatively associated with the composite cognitive score, as was ocular pain, vision-related disability, and mental health. Opening pressure and visual function were not associated with objective cognitive impairment. We found no association between subjective and objective cognitive impairment.

Conclusions and clinical implications: Patients with PTCS may be cognitively impaired, and this correlates with measures of headache burden. Studies evaluating cognitive impairment before and after remission of the headache disorder would have to be performed to investigate this relationship further. Patients with self-perception of cognitive burden are no more likely to be cognitively impaired.

Key words: pseudotumor cerebri syndrome, cognition, impairment, headache

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Introduction

Definite pseudotumor cerebri syndrome (PTCS) is characterised by papilloedema in a patient with a normal neurological exam allowing for cranial nerve abnormalities, normal brain parenchyma on neuroimaging, and elevated lumbar opening pressure (≥ 250 mm H_2O in adults) with a normal cerebrospinal fluid composition [1]. Classic symptoms including headache, transient visual obscurations, diplopia and tinnitus have been extensively reported in the literature [2–5]. While these symptoms contribute to the burden and disability associated with the syndrome, the cognitive dysfunction reported

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by these patients can often be an unrecognised source of disability, receiving little attention in the medical literature [6, 7]. In the largest trial on PTCS, 21% of 165 patients reported subjective cognitive dysfunction, which also correlated with poor health-related and vision-related quality of life [8]. This was a young (mean age 29.2) and educated (mean 14 years of schooling) population that is otherwise expected to be cognitively normal at baseline.

To date, only six studies with patient populations of one, five, 10, 30, 31 and 85 have addressed cognitive function in PTCS, with the largest study only utilising a single memory scale [6, 7, 9–12]. Most found deficits in at least one cognitive domain, typically language and memory, though there was no universal agreement [6, 7, 9–12]. None of the previous studies quantified subjective cognitive burden, though they reported it was present. The existing studies did not look extensively at confounding factors such as medication use or the relationships with the magnitude of intracranial hypertension.

The aims of our study were to: 1) determine the cognitive burden of the largest PTCS population to date; 2) compare objective results to patients' subjective cognitive dysfunction; and 3) determine how patients with objective cognitive impairment differed from patients with normal cognition in terms of a wide array of previously unstudied baseline characteristics.

Clinical rationale for study

It is necessary to further study the cognitive concerns in PTCS for several reasons. Firstly, the syndrome affects (mainly) women at an age when many are finishing training, beginning their careers, or starting families, all devastating times in life in which to be held back. Secondly, diagnosing cognitive dysfunction provides physicians with a treatment measure in addition to preservation of vision and headache control. Finally, determining predictors of cognitive dysfunction is necessary for the symptoms to be addressed adequately.

Materials and methods

Patient selection

We prospectively recruited 101 out of 146 new patients referred to the Centre for Cerebrospinal Fluid Disorders at Johns Hopkins Hospital for treatment of PTCS from August 2009 to May 2015. All patients with a diagnosis of PTCS according to published diagnostic criteria who met the inclusion criteria and who consented to cognitive testing were included, regardless of subjective cognitive deficit [1]. Patients with PTCS secondary to venous sinus stenosis were included. Patients with mental health conditions were included. Patients were otherwise healthy, and had no neurological disorder aside from PTCS.

Subjects with the following conditions were excluded: non-native English speaking, language impairment, hearing impairment, and severe visual impairment defined as visual acuity equal to or worse than 20/100 on the Early Treatment Diabetic Retinopathy Study chart, as these could have impaired reliable completion of the cognitive battery. Patients with secondary causes of PTCS including cerebrovascular abnormalities other than venous sinus stenosis (dural arterio-venous fistula), medications (lithium, tetracyclines, oral vitamin A derivatives) and medical conditions (endocrine and autoimmune disorders) were excluded, as these factors could have also influenced cognitive function [1].

History

Details regarding: age, gender, education, headache characteristics, duration of disorder, history of sleep apnoea, medication history, history of lumbar punctures and maximum opening pressure, risk factors for intracranial hypertension including use of: lithium, vitamin A or derivatives, tetracyclines, oral contraceptives, tamoxifen, and corticosteroids, and history of shunt placement were collected from participants. Educational data was missing from one patient.

Examination

Patients underwent a full neurological exam including fundoscopy to assess papilledema grade by Frisén criteria. Two neurologists (AM and OF) tested visual acuity using a retro illuminated Early Treatment Diabetic Retinopathy Study chart and corresponding LogMAR values were recorded. In the same manner, colour vision was tested using Hardy-Rand-Rittler plates.

Investigative methods

Venography with either magnetic resonance imaging or computed tomography was reviewed or ordered during the clinical encounter to assess for transverse venous sinus stenosis. Imaging data was available for 93 of 101 patients. Patients without prior lumbar puncture to document opening pressure, or with inconclusive results, underwent lumbar puncture at a separate visit, with measurement of opening pressure in the lateral decubitus position with legs extended.

Participant-completed questionnaires

Participants completed questionnaires including: the Headache Impact Test (HIT-6), a six item scale to assess headache-related disability which yields a range from 36 (no disability) to 78, where a score of 60 or more is considered severe headache-related disability [13]; the Numerical Rating Pain Scale (NRS) where 0 indicates the absence of pain, while 10 represents the most intense pain possible; the STOP-Bang screening tool for sleep apnoea, in which the presence of three or more characteristics indicates high risk for the condition [14]; the Prospective and Retrospective Memory Questionnaire (PRMQ) to assess for subjective memory failures in everyday situations, where scores range from 16 to a maximum impairment of 80, with the mean in normal adults being c.39 [15]; and the National Eye Institute Visual Function Questionnaire (VFQ 39) to assess vision-related disability [16].

Patients who scored more than 2 on the STOP-BANG questionnaire underwent formal polysomnography to determine if they had obstructive sleep apnoea, defined as an apnoea-hypopnoea index greater than five. Data from the HIT-6 was missing for six patients, from the NRS for four patients, from the VFQ39 for 11 patients, and from the PRMQ for eight patients. The PRMQ was completed by all subjects prior to initiation of the objective cognitive battery.

Cognitive testing

All participants were administered a battery of cognitive tests in a private room in the clinic. This included the following: 1) National adult reading test in English (NART) to estimate premorbid intelligence [17]; 2) Mini Mental Status examination (MMSE); 3) Digit span repetition, forward to test attention and backward to test working memory and executive function [18]; 4) Boston naming test (BNT) for confrontational naming [19]; 5) Rey auditory verbal learning test (RAVLT), a test of verbal memory [20]; 6) Clock drawing for visuospatial function [21]; 7) Trail making test (TMT), part A for psychomotor speed and B for executive function [22]; 8) Controlled oral word association task for letters CFL (COWA) to assess phonemic fluency and executive function [23]; and 9) Category fluency (animals) to test semantic fluency and memory [24]. The battery was administered to patients by a trained psychometrician. The same test instructions were used during all sessions.

Raw test scores were converted to standardised Z scores based on published norms for healthy adults and were adjusted for age, gender, and education. Impairment was defined as a Z score below 2 standard deviations (SD). Performances falling 1 SD, 1.5 SD, and 2 SD have all been suggested as cutoffs demarcating mild cognitive impairment (MCI) in various studies [25]. We chose a conservative cutoff of 2 SD in order to strike a balance between reliability, sensitivity, and specificity. A more radical cutoff of 1 SD in our patient population would have classified the vast majority of our subjects as impaired. We defined MCI-single domain when participants scored in the impaired range in one cognitive test, and MCI multi-domain when performance was impaired in two or more tests [25]. To provide more stable measures of the underlying abilities that can be compared across individuals, composites were formed with unit-weighted Z scores of constituent tests as recommended by Ackerman and Cianciolo and Riordan [26, 27]. A composite cognitive Z score was determined from the mean of tests 2 to 9 inclusive [28].

Statistical analysis

Statistical analysis was performed using Stata 15.1 software (StataCorp LLC). To compare the characteristics between the cognitively normal and the impaired, two sample t-tests or Mann-Whitney U tests (for variables not normally distributed as indicated by the Shapiro-Wilk test) were used for continuous variables and chi-square tests or Fisher's exact tests were used for categorical variables. Simple linear regression models with robust standard error estimates were carried out respectively to evaluate the associations between the composite cognitive Z scores and the baseline factors that could predict cognitive dysfunction. A multiple linear regression model was generated using backward-stepwise selection with likelihood-ratio tests. The predictors for the backward-stepwise selection included disease duration, education, NRS score, Max OP, VA, HIT-6 score, narcotic use, acetazolamide use, and VFQ Mental Health. The considerations for choosing the variables were clinical significance, relatively high association from simple linear regression, low correlation with other variables, and fewer missing values. A p value of 0.05 or less was considered statistically significant. Correlation between Trail Making Test scores with headache and visual function, and between subjective total, retrospective, and prospective memory scores and RAVLT results were explored using Spearman's rank correlation.

Institutional review board approval

This study was approved by the Johns Hopkins Medical Institutions' Institutional Review Board. All subjects gave written informed consent for participation. The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki. No formal prospective protocol was registered.

Results

Demographics

One hundred and one subjects were enrolled. Baseline characteristics of the sample, divided into groups with and without objective cognitive impairment, are set out in Table 1. There were no demographic differences between the groups.

Objective cognitive impairment in PTCS

Eight-six patients completed the entire cognitive battery. Results from one test were missing for 14 patients and results from two tests were missing for one patient. All 101 patients were included in the analysis. More than half of the subjects (n = 55) had MCI when compared to published age-, gender-, and education-adjusted norms. Thirty patients (29.7%) demonstrated MCI in a single domain, and 25 (24.8%) showed multi-domain MCI. Significantly fewer patients with MCI had venous sinus stenosis on head imaging. But other than this, the groups did not differ (Tab. 1).

When analysed with simple regression models, we found negative associations between composite cognitive score and headache intensity and HIT-6 (beta coefficients = –0.088, –0.016, p = 0.013, p = 0.021, respectively). We found positive associations between composite cognitive score and VFQ39 total, mental health and ocular pain subscores (beta coefficients = 0.014, 0.009 and 0.01, p = 0.02, 0.016, and 0.002, respectively) (Tab. 2). With this model, there were no statistically significant associations between composite cognitive score and duration of disease, body mass index,

Table 1. Baseline characteristics of PTCS patients with and without cognitive impairment

Characteristic	Without objective cognitive impairment	With objective cognitive impairment	P value
	n = 46	n = 55	
Age (mean ± SD)	35.6 ± 9.4	32.6 ± 8.4	0.094
Female (%)	40 (87%)	52 (94.5%)	0.29
Education, yrs, median (IQR)	14 (13, 16)	14 (12, 16)	0.51
Duration of disease, yrs, median (IQR)	1.0 (0.33, 2.0)	1.0 (0.25, 2.0)	0.96
BMI kg/m^2 (mean ± SD)	35.6 ± 7.3	36.8 ± 9.3	0.51
Sleep apnoea (%)	9 (19.6%)	9 (16.4%)	0.68
MRI-VSS (%)	35 (83.3%)	30 (61.2%)	0.020
Headache intensity, NRS, median (IQR)	7 (5, 8)	8 (6, 9)	0.15
HIT-6 Score, median (IQR)	62.0 (54.0, 66.0)	66.0 (58.5, 71.0)	0.053
Max OP in cm H_2O (mean ± SD)	35.2 ± 10.8	37.3 ± 9.6	0.31
VA, median (IQR)	–0.05 (–0.09, 0.00)	–0.02 (–0.09, 0.04)	0.26
CV, median (IQR)	10.0 (9.75, 10.0)	10.0 (9.75, 10.0)	0.81
PA (mean ± SD)	1.75 ± 1.09	1.38 ± 1.19	0.11
Total VFQ39, median (IQR)	82.2 (73.3, 90.9)	79.2 (68.2, 90.2)	0.35
VFQ Mental Health, median (IQR)	82.5 (50.0, 90.0)	75.0 (50.0, 90.0)	0.18
VFQ Ocular Pain (mean ± SD)	63.4 ± 22.0	53.9 ± 27.6	0.077
PRMQ (mean ± SD)	39.9 ± 12.9	39.0 ± 14.2	0.76
Narcotic use (%)	4 (8.7%)	6 (10.9%)	0.75
Acetazolamide use (%)	19 (41.3%)	31 (56.4%)	0.13
Topiramate use (%)	5 (10.9%)	4 (7.3%)	0.73

IQR — interquartile range; BMI — body mass index; MRI-VSS — presence of venous sinus stenosis on head imaging; NRS — numerical rating pain scale; HIT-6 — Headache Impact Test 6 score; OP, CSF — opening pressure; VA — visual acuity; CV — colour vision; PA — Frisén papilloedema grade; VFQ-39 — Visual Function Questionnaire 39 score; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score

sleep apnoea, presence of venous sinus stenosis, maximum opening pressure, mean visual acuity, mean colour contrast, narcotic use, acetazolamide use, topiramate use, or PRMQ score (Tab. 2). A multiple linear regression model adjusting for maximum opening pressure and mental health score showed that as headache intensity increased by one point, composite Z score decreased by 0.077 points (95% CI: –0.149, –0.005, p = 0.037). (Tab. 2, Fig. 1).

Supplementary Table 1 demonstrates raw and Z score ranges for each cognitive test, as well as the percentage of patients scoring 2 SD below the normative cut-off on each test. More patients scored below the cutoff on BNT and TMT part B than any other tests. Supplementary Table 2 shows correlations between TMT and headache intensity and visual function measures. We found negative correlations between TMT and headache intensity and visual acuity, but not colour vision or papilloedema grade.

Subjective cognitive impairment in PTCS

On average, subjective assessment of cognitive impairment in the whole cohort was similar to published norms as evidenced by a total PRMQ T score of 49.9 (Tab. 3). The mean total PRMQ score in the general, healthy adult population is 38.8, and higher scores represent greater subjective impairment [15]. In our study, 11.8% of subjects scored more than 2 SD above this published mean, reflecting more than average subjective concerns over memory (Tab. 4). There was no difference in PRMQ results comparing patients with or without MCI (Tab. 1). When analysed with regression methods, there was a trend but no statistically significant correlation with PRMQ scores and composite cognitive Z score (Tab. 2), although we found negative correlations between the total, retrospective, and prospective PRMQ scores and the RAVLT results (Suppl. Tab. 3).

Discussion

To the best of our knowledge, this was the first study to examine multiple domains of cognition in a population of more than 31 PTCS patients. Over half of our patients showed at least single-domain MCI compared to published norms. Our results agree with previous studies finding objective cognitive impairment in PTCS [6,7, 10–12]. Objective cognitive impairment correlated only with headache

Table 2. Simple and multiple regression model results for associations between composite cognitive Z score and NRS pain score, HIT-6 score, and other potential factors

Characteristic	Simple linear regression model			Multiple linear regression model		
	Coefficient	95% Confidence interval	P value	Coefficient	95% Confidence interval	P value
Age	0.004	–0.017, 0.024	0.707			
Female vs. male	0.138	–0.607, 0.883	0.714			
Education, yrs	0.070	0.009, 0.130	0.024			
Duration of disease, yrs	–0.043	–0.102, 0.015	0.147			
BMI kg/m^2	–0.001	–0.021, 0.019	0.915			
Sleep apnoea: yes vs. no	0.062	–0.378, 0.503	0.780			
MRI-VSS: yes vs. no	0.275	–0.145, 0.696	0.197			
Headache intensity, NRS	–0.088	–0.157, –0.019	0.013	–0.077	–0.149, –0.005	0.037
HIT-6 Score	–0.016	–0.030, –0.003	0.021			
Max OP in cmH_20	–0.011	–0.028, 0.006	0.215	–0.013	–0.029, 0.003	0.111
VA	–0.659	–1.615, 0.296	0.174			
CV	0.058	0.060,0.176	0.332			
Total VFQ39	0.014	0.002, 0.026	0.020			
VFQ Mental Health	0.009	0.002, 0.016	0.016	0.007	–0.001, 0.015	0.083
VFQ Ocular Pain	0.010	0.004, 0.016	0.002			
PRMQ	–0.009	–0.021, 0.003	0.130			
Narcotic use: yes vs. no	–0.405	–1.001, 0.191	0.181			
Acetazolamide use: yes vs. no	–0.232	–0.546, 0.082	0.146			
Topiramate use: yes vs. no	–0.148	–0.929, 0.634	0.709			

BMI — body mass index; CV — mean colour vision; HIT-6 — Headache Impact Test 6 score; MRI-VSS — presence of venous sinus stenosis on head imaging; NRS — numerical rating pain scale; OP, CSF — opening pressure; PA — mean Frisén papilloedema grade; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score; VA — mean visual acuity; VFQ-39 — total Visual Function Questionnaire 39 score

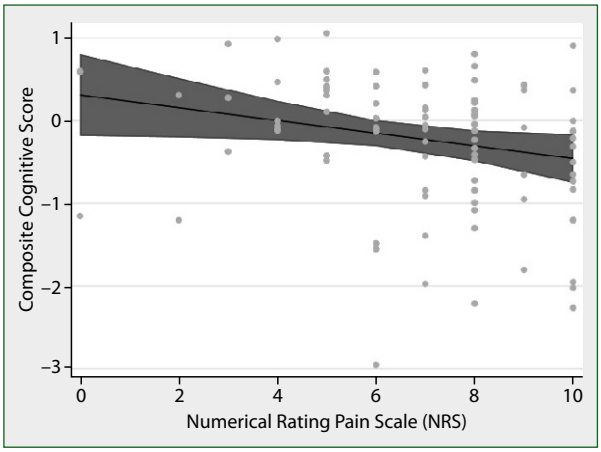

Figure 1. Relationship between composite cognitive score and headache severity. Predictive margins and 95% confidence intervals are from multiple regression model adjusting for maximum opening pressure and VFQ Mental Health

burden, ocular pain, mental health, and visual quality of life, and surprisingly did not correlate with self-perception of cognitive impairment.

Table 3. Prospective and retrospective memory scores in our PTCS patients compared to published norms

	T score
Total PRMQ score ± SD	49.9 ± 14.8
Retrospective PRMQ score ± SD	51.8 ± 13.8
Prospective PRMQ score ± SD	46.5 ± 14.9

This was the first study to quantify patients' impressions of cognitive deficit and compare that to objective cognitive burden. Of the six previous studies on the subject, five reported that patients did note cognitive difficulties [6, 7, 9, 10, 12]. In Kaplan's case report, the single patient self-reported difficulty with concentration and memory, prompting the case study, and this was corroborated by the report of "very high level of difficulty with cognitive tasks" on the administered Chronic Pain Inventory [9]. All five of the patients studied by Sorensen et al. self-reported problems with concentration, learning, and memory, as did half of the patients studied by Kharkar, over half of the patients studied by Yri, and all 30 patients studied by Zur [6, 7, 10, 12]. These were all self-reported concerns of cognitive difficulty, presumably by interview, as self-report

Table 4. Percentage of our patients scoring > 2SD above published norms in PRMQ

	A mean	B SD	C Range	D SEM_{xt}	E Patients scoring > 2SD above mean
Total PRMQ score	38.88	9.15	17–67	2.95	11.8%
Prospective score	20.18	4.91	8–35	3.36	12.9%
Retrospective score	18.69	4.98	8–33	3.58	6.5%

PRMQ — prospective and retrospective memory questionnaire; PTCS — pseudotumor cerebri syndrome
Subjective total, prospective, and retrospective memory burden reported by patients on PRMQ. For ease of interpretation, Table 3a reports scales as T scores, determined from conversion of raw scores based on published norms. Table 3b (columns A to D) represents published norms for PRMQ, and column E reflects percentage of our subjects scoring in a symptomatic range on this measure of subjective cognitive impairment
PTCS — pseudotumor cerebri syndrome; PRMQ — prospective and retrospective memory questionnaire

scales were not mentioned in any study other than Kaplan's [9]. In the large cohort of the Idiopathic Intracranial Hypertension Treatment Trial, the primary aim of which was not to study cognitive impairment, this self-report (no scale) of cognitive difficulty was much lower, at 21% of 165 patients [8]. In contrast to these groups, which unanimously support self-perception of cognitive difficulties in PTCS, we showed that when a formal questionnaire regarding prospective and retrospective memory is administered (rather than directly asking subjects whether they experienced cognitive difficulties), only a minority of subjects showed subjective cognitive impairment. Specifically, less than 12% of our patients scored 2 SD above the mean level of subjective cognitive impairment (referring to total PRMQ score), despite over half the sample showing objective MCI, indicating a possible lack of awareness of the deficit. Other groups had clinically noted a lack of self-awareness in patients with PTCS, raising their suspicion of prefrontal dysfunction [10].

The secondary aim of our study was to explore the predictors of cognitive impairment. In this study, objective cognitive impairment correlated with headache severity at the time of testing, headache-related disability, and ocular pain, all congruent findings. Severity of headache was reported in only one previous study. It is interesting in light of our results that Yri et al. found no association between headache and cognitive performance [10]. It is reported that 71% of Yri's patients had headache at the time of initial testing, with the mean NRS pain score being 2.3 [10]. This discrepancy may be accounted for by the fact that all our patients suffered more severe headache at the time of testing, with mean NRS pain score of 8 in patients with MCI. Taking our results into account, it is also interesting that Zur et al. found cognitive impairment in a PTCS population that was free from severe or chronic headache [12]. This discrepancy could potentially be explained by our larger sample size, and our more stringent definition of cognitive impairment.

It is not surprising that our two measures of headache severity correlated with overall cognitive burden. The evidence for long-term cognitive impairment in migraine has been contradictory, but it is clear that migraineurs experience ictal cognitive impairment, and possible that the ones most affected by headache experience interictal cognitive difficulties as well [29]. Studies comparing migraineurs to subjects with non-migraine headache and non-headache chronic pain found similar mild deficits in cognition, suggesting that poor performance was a factor of general pain rather than intrinsic to the headache disorder [30, 31]. It is often implied that cognitive dysfunction in chronic pain is related to depression [30]. Indeed, depression is common in migraine [32] and more common in PTCS then normal weight controls, and more severe compared to weight-matched controls [33]. However, depression was not associated with poor cognitive performance in Yri's sample [10], and while our simple linear regression model found a correlation between cognitive impairment and worse mental health, this finding was no longer significant in the multiple regression model adjusting for headache severity. Larger cohorts or more detailed measures of mental health would be needed to explore this relationship in the future.

We wanted to understand whether factors intrinsic to the intracranial hypertension itself could predict cognitive dysfunction. This encompasses the risk factors for the disorder — namely BMI, obstructive sleep apnoea, and venous sinus stenosis (when primary), the consequences — including opening pressure, visual function, papilloedema grade, and visual quality of life, and the treatments — specifically medications which could impact cognition, including acetazolamide, topiramate, and narcotics.

In agreement with the earlier work, we found no correlation of cognitive impairment with patient BMI, which is surprising given previous, albeit inconsistent, associations of obesity with cognitive dysfunction in the general population [10, 12, 24]. It is possible that if we had used markers of central obesity, such as waist circumference or weight-to-hip ratio, our results would have differed.

Likewise, we found no relationship between the comorbidity of sleep apnoea and cognitive dysfunction, a surprising new finding given the degree of daytime fatigue, and known reversible cognitive dysfunction that is classically experienced in the sleep disorder [35]. Future studies could explore this relationship in more detail and in larger cohorts, stratifying the patients according to apnoea-hypopnoea-index, and treatment status (with positive airway pressure).

We considered the final risk factor for PTC to be venous sinus stenosis. Most of our patients did have venous sinus stenosis on initial imaging. We expected that the possible venous congestion occurring as a consequence of venous sinus stenosis would have led to cognitive impairment, akin to other conditions described causing venous congestive encephalopathy [36, 37]. We were surprised to find that significantly more of our patients without MCI had stenosis. It is possible that no relationship existed after all, as this difference did not hold up in our simple regression model, or that simply too many of our patients had venous sinus stenosis, making it difficult to discern differences. A future direction could include stratifying patients by primary versus secondary venous sinus stenosis, if known.

The next set of characteristics pertained directly to intracranial hypertension. We did not find any correlation between the composite cognitive score and maximum opening pressure. Yri et al. performed both cognitive testing and lumbar puncture at baseline and 3-month follow up in 31 subjects with PTCS, and found no correlation between change in cognitive performance and change in intracranial pressure, which supports our finding [10]. We demonstrated that objective cognitive impairment, as measured by the composite cognitive score, correlated with worse visual quality of life, especially in the domain of ocular pain, despite no correlation to visual acuity or colour vision. Earlier studies showed that higher headache-related disability correlated with visual quality of life in pseudotumor cerebri [8] and that visual quality of life was substantially reduced in migraineurs without PTCS, especially in the domain of ocular pain [38], so our finding was not surprising in the context of our other results highlighting the effect of headache.

Finally, we studied the relationship between cognitive impairment and potentially confounding medications namely acetazolamide, topiramate, and narcotics, and found none. This is in agreement with previous work looking at acetazolamide [12].

Our results could support additional diagnostics and treatments in the management of PTCS. Consideration should be given to including at least screening cognitive tests in the standard management of PTCS, considering the majority of our patients did not recognise cognitive burden, despite it being present. Secondly, our results cautiously support the treatment of the headache disorder associated with PTCS independent of the treatments aimed at reducing intracranial pressure. While acetazolamide has been proven to improve visual outcomes in PTCS, it does not address the coexistent headache disorder, which often needs separate treatment [39, 40].

Our study has several limitations. This was a non-blinded study, potentially affecting subjects' performance. Secondly, while our study was controlled using published normative data for cognitive testing in healthy adults, we did not control for the presence of chronic headache. This is being addressed in an ongoing study that is quantifying the cognitive burden in a population with chronic daily headaches and will be reported separately. Thirdly, we did not specifically evaluate depression or anxiety, although we administered the VFQ39 which quantifies level of worry, frustration, irritability, isolation, and lack of control, and these are reported as the Mental Health subscore [16]. Finally, we did not perform follow up cognitive testing after resolution of headache to determine reversibility of deficits.

Nevertheless, given the rarity of this disorder and the large number of subjects enrolled, we were able to identify prevalence and predictors of cognitive impairment in subjects with PTCS.

Conclusions, clinical implications, future directions

Single-domain and multi-domain mild cognitive impairment is present in pseudotumor cerebri syndrome, and correlates with headache and ocular pain burden, but not with self-perception of deficit.

Measures representing intracranial hypertension such as cerebrospinal fluid opening pressure, papilloedema grade, and visual function did not correlate with cognitive impairment. Future controlled studies are needed with cognitive testing before and after headache remission in order to understand the full extent of the demonstrated relationships.

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References

1. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2013; 81(13): 1159–1165, doi: 10.1212/WNL.0b013e3182a55f17, indexed in Pubmed: 23966248.
2. Ambika S, Arjundas D, Noronha V, et al. Clinical profile, evaluation, management and visual outcome of idiopathic intracranial hypertension in a neuro-ophthalmology clinic of a tertiary referral ophthalmic center in India. Ann Indian Acad Neurol. 2010; 13(1): 37–41, doi: 10.4103/0972-2327.61275, indexed in Pubmed: 20436745.
3. D'Amico D, Curone M, Erbetta A, et al. Intracranial idiopathic hypertension: 1-year follow-up study. Neurol Sci. 2014; 35 Suppl 1: 177–179, doi: 10.1007/s10072-014-1765-x, indexed in Pubmed: 24867861.
4. Liu IH, Wang AG, Yen MY. Idiopathic intracranial hypertension: clinical features in Chinese patients. Jpn J Ophthalmol. 2011; 55(2): 138–142, doi: 10.1007/s10384-010-0907-9, indexed in Pubmed: 21400059.
5. Pollak L, Zohar E, Glovinsky Y, et al. Reevaluation of presentation and course of idiopathic intracranial hypertension–a large cohort comprehensive study. Acta Neurol Scand. 2013; 127(6): 406–412, doi: 10.1111/ane.12060, indexed in Pubmed: 23278763.
6. Sørensen PS, Thomsen AM, Gjerris F. Persistent disturbances of cognitive functions in patients with pseudotumor cerebri. Acta Neurol

Scand. 1986; 73(3): 264–268, doi: 10.1111/j.1600-0404.1986.tb03273.x, indexed in Pubmed: 3716764.
7. Kharkar S, Hernandez R, Batra S, et al. Cognitive impairment in patients with Pseudotumor Cerebri Syndrome. Behav Neurol. 2011; 24(2): 143–148, doi: 10.3233/BEN-2011-0325, indexed in Pubmed: 21606575.
8. Digre KB, Bruce BB, McDermott MP, et al. NORDIC Idiopathic Intracranial Hypertension Study Group. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH Treatment Trial results. Neurology. 2015; 84(24): 2449–2456, doi: 10.1212/WNL.0000000000001687, indexed in Pubmed: 25995055.
9. Kaplan CP, Miner ME, McGregor JM. Pseudotumour cerebri: risk for cognitive impairment? Brain Inj. 1997; 11(4): 293–303, doi: 10.1080/026990597123601, indexed in Pubmed: 9134204.
10. Yri HM, Fagerlund B, Forchhammer HB, et al. Cognitive function in idiopathic intracranial hypertension: a prospective case-control study. BMJ Open. 2014; 4(4): e004376, doi: 10.1136/bmjopen-2013-004376, indexed in Pubmed: 24713214.
11. Arseni C, Simoca I, Jipescu I, et al. Pseudotumor cerebri: risk factors, clinical course, prognostic criteria. . Rom J Neurol Psychiatry. 2016; 30(2): 115–132, indexed in Pubmed: 1520600.
12. Zur D, Naftaliev E, Kesler A. Evidence of multidomain mild cognitive impairment in idiopathic intracranial hypertension. J Neuroophthalmol. 2015; 35(1): 26–30, doi: 10.1097/WNO.0000000000000199, indexed in Pubmed: 25383589.
13. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003; 12(8): 963–974, doi: 10.1023/a:1026119331193, indexed in Pubmed: 14651415.
14. Chung F, Yegneswaran B, Liao Pu, et al. STOP Questionnaire. Anesthesiology. 2008; 108(5): 812–821, doi: 10.1097/aln.0b013e31816d83e4.
15. Crawford JR, Smith G, Maylor EA, et al. The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. Memory. 2003; 11(3): 261–275, doi: 10.1080/09658210244000027, indexed in Pubmed: 12908675.
16. Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol. 1998; 116(11): 1496–1504, doi: 10.1001/archopht.116.11.1496, indexed in Pubmed: 9823352.
17. Crawford JR, Moore JW, Cameron IM. Verbal fluency: a NART-based equation for the estimation of premorbid performance. Br J Clin Psychol. 1992; 31(3): 327–329, doi: 10.1111/j.2044-8260.1992.tb00999.x, indexed in Pubmed: 1393161.
18. Weschler D. WMS-III Administration and Scoring Manual. The Psychological Corportation/Harcourt Brace & Co. ; 1997.
19. Tombaugh TN, Hubley AM. The 60-item Boston Naming Test: norms for cognitively intact adults aged 25 to 88 years. J Clin Exp Neuropsychol. 1997; 19(6): 922–932, doi: 10.1080/01688639708403773, indexed in Pubmed: 9524887.
20. Savage R. Rey auditory-verbal learning test: The effects of age and gender, and norms for delayed recall and story recognition trials. Archives of Clinical Neuropsychology. 1992; 7(5): 407–414, doi: 10.1016/0887-6177(92)90153-e.
21. Rouleau I, Salmon DP, Butters N. Longitudinal analysis of clock drawing in Alzheimer's disease patients. Brain Cogn. 1996; 31(1): 17–34, doi: 10.1006/brcg.1996.0022, indexed in Pubmed: 8790932.
22. Tombaugh T. Trail Making test A and B: normative data stratified by age and education. Archives of Clinical Neuropsychology. 2004; 19(2): 203–214, doi: 10.1016/s0887-6177(03)00039-8.
23. Ross TP, Furr AE, Carter SE, et al. The psychometric equivalence of two alternate forms of the Controlled Oral Word Association Test. Clin Neuropsychol. 2006; 20(3): 414–431, doi: 10.1080/13854040590967153, indexed in Pubmed: 16895856.
24. Acevedo A, Loewenstein DA, Barker WW, et al. Category fluency test: normative data for English- and Spanish-speaking elderly. J Int Neuropsychol Soc. 2000; 6(7): 760–769, doi: 10.1017/s1355617700677032, indexed in Pubmed: 11105466.
25. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry. 2009; 17(5): 368–375, doi: 10.1097/JGP.0b013e31819431d5, indexed in Pubmed: 19390294.
26. Ackerman PL, Cianciolo AT. Cognitive, perceptual-speed, and psychomotor determinants of individual differences during skill acquisition. J Exp Psychol Appl. 2000; 6(4): 259–290, doi: 10.1037//1076-898x.6.4.259, indexed in Pubmed: 11218338.
27. Riordan H. Constructing Composites to Optimize Cognitive Outcomes. J Clin Stud. 2017; 9(2): 40–45.
28. Donohue MC, Sperling RA, Salmon DP, et al. Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing, Alzheimer's Disease Neuroimaging Initiative, Alzheimer's Disease Cooperative Study. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol. 2014; 71(8): 961–970, doi: 10.1001/jamaneurol.2014.803, indexed in Pubmed: 24886908.
29. Gil-Gouveia R, Martins IP, Gil-Gouveia R, et al. A subjective cognitive impairment scale for migraine attacks. The MIG-SCOG: development and validation. Cephalalgia. 2011; 31(9): 984–991, doi: 10.1177/0333102411408359, indexed in Pubmed: 21628438.
30. Gil-Gouveia R, Martins IP, Martins IP, et al. Migraine, headaches, and cognition. Headache. 2012; 52(10): 1471–1482, doi: 10.1111/j.1526-4610.2012.02218.x, indexed in Pubmed: 22830358.
31. Bell BD, Primeau M, Sweet JJ, et al. Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. Archives of Clinical Neuropsychology. 1999; 14(4): 389–399, doi: 10.1093/arclin/14.4.389.
32. Domitrz I, Lipa A, Rożniecki J, et al. Treatment and management of migraine in neurological ambulatory practice in Poland by indicating therapy with monoclonal anti-CGRP antibodies. Neurol Neurochir Pol. 2020; 54(4): 337–343, doi: 10.5603/PJNNS.a2020.0054, indexed in Pubmed: 32687594.
33. Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life. Neurology. 2000; 54(2): 319–324, doi: 10.1212/wnl.54.2.319, indexed in Pubmed: 10668690.
34. Buie JJ, Watson LS, Smith CJ, et al. Obesity-related cognitive impairment: The role of endothelial dysfunction. Neurobiol Dis. 2019; 132: 104580, doi: 10.1016/j.nbd.2019.104580, indexed in Pubmed: 31454547.
35. Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. Am J Geriatr Psychiatry. 2016; 24(6): 496–508, doi: 10.1016/j.jagp.2016.01.134, indexed in Pubmed: 27139243.
36. Dijk Jv, Willinsky R. Venous congestive encephalopathy related to cranial dural arteriovenous fistulas. Neuroimaging Clinics of North America. 2003; 13(1): 55–72, doi: 10.1016/s1052-5149(02)00063-1.

37. Wang HC, Lin WC, Kuo YL, et al. Factors associated with brainstem congestive encephalopathy in dural arterio-venous fistulas. Clin Neurol Neurosurg. 2009; 111(4): 335–340, doi: 10.1016/j.clineuro.2008.11.004, indexed in Pubmed: 19101079.
38. Hanson LL, Ahmed Z, Katz BJ, et al. Patients with migraine have substantial reductions in measures of visual quality of life. Headache. 2018; 58(7): 1007–1013, doi: 10.1111/head.13330, indexed in Pubmed: 29877580.
39. Bruce BB, Digre KB, McDermott MP, et al. NORDIC Idiopathic Intracranial Hypertension Study Group, NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014; 311(16): 1641–1651, doi: 10.1001/jama.2014.3312, indexed in Pubmed: 24756514.
40. Raggi A, Marzoli SB, Chiapparini L, et al. Headache frequency and symptoms of depression as predictors of disability in patients with idiopathic intracranial hypertension. Neurol Sci. 2018; 39(Suppl 1): 139–140, doi: 10.1007/s10072-018-3361-y, indexed in Pubmed: 29904836.