Idiopathic intracranial hypertension is associated with cognitive dysfunction — a prospective case-control study

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Idiopathic intracranial hypertension is associated with cognitive dysfunction — a prospective case-control study

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KEY WORDS

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ABSTRACT

Objective: To explore the extent and nature of cognitive deficits in patients with idiopathic intracranial hypertension at time of diagnosis and after three months of treatment.

Design: Prospective case-control study.

Setting: Neurological department, ophthalmological department and a tertiary headache referral clinic at a Danish university hospital**.**

Participants: Thirty-one patients with definite idiopathic intracranial hypertension referred from June 2011– February 2013 and included within one week of diagnostic intracranial pressure measurement. Twenty-nine patients completed re-examined at the 3-month follow-up. At time of testing none of the patients took medication potentially affecting cognitive function. Controls were 31 healthy age- and sex-matched volunteers from the local community.

Outcome measures: Executive function, working memory, visuospatial memory, processing speed, attention, and reaction time assessed by a comprehensive neuropsychological test battery consisting of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB)) and paper-and-pencil tests.

Results: Patients with idiopathic intracranial hypertension performed significantly worse than controls in four of six cognitive domains ($p \leq .02$). Deficits were most pronounced in reaction time (1.45 SD below controls 95% CI 2.10 to 0.85) and processing speed (1.45 SD below controls 95% CI 2.08 to 0.81). Despite marked improvement in intracranial pressure and headache, re-examination showed persistent cognitive dysfunction three months after diagnosis and start of treatment.

Conclusions: We demonstrate for the first time in a well-defined cohort of patients that Idiopathic intracranial hypertension may be associated with cognitive dysfunction. This may explain the functional disability of patients with Idiopathic intracranial hypertension. A focused

multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with IIH.

ARTICLE SUMMARY

Strengths and limitations of this study

- The first study to assess a broad range of cognitive functions in more than 10 patients
- Prospective controlled design and a well defined study population
- Controls were matched for age, sex and premorbid intelligence
- The study was non-blinded and controls were not matched for Body Masse Index (BMI)
- Cognitive assessment by an automated computerized test battery reduced the influence of the non-blinded observer

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is characterized by raised intracranial pressure (ICP) without an identifiable cause primarily affecting young obese women. The estimated incidence in the obese population is 20 per 100,000 which is 20-fold the incidence in normal-weight individuals.[1;2] Prevalence is predicted to rise in the wake of the global obesity epidemic.[3]

Due to predilection for young individuals of working age the socioeconomic consequences of IIH are substantial. In USA alone the estimated annual costs exceed $444 million (> $17,000 /patient).[4] In addition to direct medical cost the major expenses was loss of wages caused by patients having to give up work or change profession due to IIH. Loss of income due to IIH is reported by 48% of patients,[4] but the exact cause of this substantial disability is yet unknown.

Despite the obvious threat to visual function, compliance with long-term treatment is surprisingly poor. In clinical settings we experience substantial lack of initiative and self-care which could indicate prefrontal dysfunction. While numerous studies describe the visual and headache-related complications of IIH, very little is known about the cognitive implications of the disease and their socioeconomic consequences.[5-8]

The aim of this case-control study is to prospectively explore the extent and nature of cognitive deficits at time of IIH-diagnosis and after three months of treatment.

METHODS

Subjects

We recruited 31 consecutive patients with IIH referred to the Department of Neuro-Ophthalmology, the Department of Neurology or the Danish Headache Center, Glostrup Hospital from June 2011–

February 2013. Sample size was determined by the number of cases referred in the inclusion period. Twenty-eight of the patients were newly diagnosed with IIH, three patients had well-defined relapse of IIH after a minimum of 10 months (range 10-26 months) of medication-free remission (resolved headache and papilledema). All patients had definite IIH according to the diagnostic criteria.[9;10] We included only patients that could be tested within seven days of confirmed diagnosis. Exclusion criteria were: other disorders or medication that could potentially affect cognition, decreased visual aquity, or language skills (Danish) deemed insufficient for participation in the cognitive assessment. Thirty-one healthy and headache free (defined as less than 4 headache days/month) controls, matched for age and sex, were recruited by advertising at Glostrup Hospital and on the website forsogspersonen.dk. Healthy controls were tested only once and did not have a lumbar puncture performed. Otherwise the cognitive examination program for patients and controls was identical.

Standard protocol approvals, registration and patients consents

All participants gave written, informed consent to participate in the study. The study was conducted in accordance with the declaration of Helsinki and approved by the Regional Ethics Committee.

General examination

At time of diagnosis patients underwent a complete neurological examination including MR/CT-imaging with venous sequences. All but one patient underwent thorough standardized neuro-ophthalmological examination.[11] The remaining patient did not participate in the neuro-opthalmological evaluation in spite of numerous invitations. A general ophthalmological examination was, however, performed at the local referring ophthalmological department.

Treatment

After diagnostic lumbar puncture and after cognitive testing was completed, treatment with acetazolamide was initiated. From baseline to 3-month follow-up doses were individually adjusted at doses of 750-2225 mg/day. Due to intolerable side effects acetazolamide was replaced by topiramate, 125 mg/day in one patient. Treatment with acetazolamide and topiramate was paused respectively three and seven days before the 3-month follow-up examinations.

Infrequent (<14 days/month) use of simple analgesics (paracetamol and/or acetylsalicylic acid) was allowed. Treatment did not include use of opiate analgesics or tranquilizers.

Weight-loss was strongly recommended and patients were offered dietician consultations.

ICP

ICP was measured at baseline and at the 3-month follow-up. In one patient ICP was measured by direct intracranial pressure monitoring. In the remaining patients (n=30) ICP was measured by standardized lumbar puncture manometry. Patients were placed in lateral decubital position, had their legs straightened and were given a minimum of 10 min to relax before a stabilized pressure was recorded.

Cognitive testing

We assessed cognitive function by a neuropsychological test battery of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB))[12] and paper-and-pencil tests.

Paper-and-pencil tests: (a) **Rey – Osterreith's Complex Figure Test**, testing visuospatial memory; (b) **Trail Making Test A and B**, primarily testing psychomotor speed; (c) **Symbol Digit Modalities Test,** testing psychomotor speed; (d) **Verbal Fluency Test,** testing verbal semantic and phonological

fluency. The letters "S" and "A" and the categories "animals" and "items in a supermarket" were used.

CANTAB computerized tests: (e) **Motor screening test** to familiarize subjects with the touch screen; (f) **Spatial Span**, assessing visuospatial working memory span; (g) **Spatial Working Memory**, testing the ability to retain and manipulate spatial information in working memory; (h) **Stockings of Cambridge**, assessing spatial planning ability; (i) **Intra-Extra Dimensional Set Shift,** testing cognitive flexibility, requiring the formation and shifting of attentional set; (j) **Reaction Time**, assessing motor and reaction time latencies; (k) **Rapid Visual Information Processing**, testing sustained attention with a working memory load.

The **Danish Adult Reading Test** (Danish version of the National Adult Reading Test) was applied as an estimate of premorbid intelligence.[13]

The test battery was administered in a fixed order by the same physician (HY), instructed and trained by experienced neuro-psychologists (HF, BF). To ensure uniform test instructions we used a written instruction-manual during all sessions. Headache intensity at time of testing was recorded by a 10-point Visual Analogue Scale (VAS). Patients were re-tested at the 3-month follow-up.

Statistical analysis

Statistical analyses were conducted using SAS 9.3. Significance levels were set at 0.05. Non-normal distributed data were logarithmically transformed to reduce skewness. Categorical data were investigated by Chi-square test, Fishers' exact test and McNemar test.

Test-scores of patients and healthy controls were compared using a linear mixed model adjusting for education and headache at time of testing. Changes in patient test-scores from baseline to follow-up were analyzed in a linear mixed model for paired data adjusting for headache at time of testing. Test performance in patients with normalized ICP at follow-up and patient with continuous elevated ICP

was compared in a mixed model using ICP ≤25 cmH_2O and ICP<25 cmH_2O as a binary categorical variable. To avoid effects of multiple comparisons in the analyses of cognitive function, the analyses were performed in mixed linear models including all 19 subtest scores into the same model.

For comparability of test-scores and evaluation of effect sizes, test-scores were standardized into z-scores. Z-scores were based on performance of the healthy controls which by definition had a mean scale score of zero and SD set to one. All scales were computed so that a higher z-score indicate better performance.

We used standardized test-scores to create composite domain scores, calculated by grouping selected tests, based on which cognitive domain they theoretically represented. Z-scores for cognitive domains were averaged and re-standardized based on the composite domain average and standard deviation of healthy controls.

Although they spoke Danish fluently, Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from statistical analysis as these test are potentially influenced by language-fluency and familiarity with the Latin alphabet. In domain construction the average of the remaining tests was used to determine the domain score.

RESULTS

Demographics and clinical characteristics at baseline

Patients and healthy controls did not differ in demographics, household income, educational level or premorbid intelligence level (Table 1). However, patient had significantly higher BMI and slightly less education counted in years than healthy controls.

Headache at the time of testing was reported by the majority of patients, but by none of the controls (Table 1). General headache disability in patients was heterogeneous. Nine patients fulfilled the criteria of chronic headache (≥15 days/month for 3 months)[10], four patients had frequent headache

(mean 7.7 days/month)[10], seven had infrequent headache (<1 day /month)[10], 14 had only had headache in the weeks up until diagnosis and four patient had no headache at all. Healthy controls reported infrequent headaches with a mean frequency at 0.5 days/month.

Visual fields (Automated perimetry, Humprey 30-2) were bilaterally normal in 14 patients and normal in at least one eye in another eight patients. Seven patients had mild bilateral peripheral defects. One patient had bilateral concentric defects with remaining 15-20 central degrees of vision. In the cognitive tests this patient performed equally to the average patient. No photophobia or visual disturbances were reported during testing.

Twenty-two patients were on either short term (n=18) or long-term sick-leave (n=4), five were unemployed and three had retired from work for reasons other than IIH.

Table 1. Demographics and clinical characteristics for IIH patients at baseline and at follow-up and healthy controls

	IIH Baseline n=31	IIH Follow-up n=29	Controls n=31	Statistics p[d]	p[e]
Demographics					
Age (SD), *years*	31.0 (11.2)		30.7 (11.2)	0.91	
Gender, *m/f*	31/0		31/0		
Danish Adult Reading Test (SD), *words*	22.9 (6.8)		24.8 (5.3)	0.15	
Education (SD), *years*	11.2 (2.2)		12.8 (2.1)	**0.001**	
Educational level				0.38	
Long cycle higher (≥ 5 years), *n*	0		3		
Medium cycle higher (3–5 years), *n*	4		7		
Short cycle higher (<3years), *n*	4		4		
Vocational upper- secondary, *n*	5		3		
Student, *n*	10		10		
No education, *n*	8		4		
Household income				0.81	
High (>DKK 400,000/year), *n*	10		8		
Middle (DKK 200-400,000/year), *n*	12		12		
Low (<DKK 200,000/year), *n*	9		11		
Clinical Characteristics					
BMI (SD), kg/m^2	35.7 (6.2)	34.0 (6.0)	23.6 (4.0)	**<0.001**	**0.009**
Headache at time of testing, *n (%)*	22 (71)	14 (48)	0		
Mean headache intensity (SD), *VAS*	2.64 (2.3)	1.84 (2.4)			**0.01**
ICP ↔ cognitive testing[a] (SD), *days*	3 (2.4)	1 (1.6)			
Mean ICP[b] (SD), cmH_2O	41.0 (12.6)	25.9 (5.5)			**<0.001**
Memory difficulties[c], *n (%)*	17 (55)	18 (62)			0.42

Concentration difficulties[c], *n (%)*	20 (65)	15 (52)	0.18
Duration of IIH symptoms (SD), *months*	4.34 (5.4)		

Chi-square test was used for household income, Fishers' exact test for educational level and McNemars'test for paired categorical variables. 2-tailed T-test was used for numerical variables. Significant p-values are printed in bold. [a]Time-span between ICP measurement and cognitive testing. [b]ICP measured with intracranial pressure monitor (n=1) not included. [c]Subjective difficulties reported by the patients. p[d]: difference between patients at baseline and healthy controls. p[e]: difference between patients at baseline and follow-up.

Cognitive function in patients at baseline compared to healthy controls

IIH-patients performed significantly worse than controls in four of six cognitive domains and in 13 of 19 subtests (Table 2). The most pronounced deficits were found in the domains of processing speed and reaction time (Figure 1). Even though deficits in executive functions only reached trend levels of significance patients scored significantly worse in the subtest measuring cognitive flexibility (ID/ED errors). Likewise, patients performed significantly worse in the subtest measuring spatial working memory strategy although no overall deficits in working memory was found.

Table 2. Cognitive test scores and composite domain scores at baseline compared to healthy controls

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	Healthy Controls			
	n=31	n=31	Z	95% CL	p
Executive function			-0.61	-1.25;0.02	0.059
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors^{log}	8.1 (0-32)	4.0 (0-25)	-0.94	-1.54;-0.35	**0.002**
Total errors adjusted^{log},	20.9 (7-177)	12.2 (7-55)	-0.91	-1.50;-0.32	**0.003**
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	10.19 (1.7)	-0.28	-0.87;0.31	0.31
Initial thinking time^{log}, *s*	6.5 (2.0-18.3)	8.2 (3.1-40.7)	0.49	-0.11;1.08	0.11
Subsequent thinking time^{log}, *s*	0.013 (0-3.7)	0.011 (0-3.0)	0.09	-0.51;0.68	0.77
Trail Making Test[a]					
Trail Making B-A^{log}, *s*	39.2 (14.7-101.1)	30.62 (16.3-98.4)	-0.56	-1.10;0.09	0.07
Working memory			-0.56	-1.19;0.08	0.08
Spatial Working Memory					
Strategy score^{log}	29.9 (20-42)	24.8 (19-40)	-0.75	-1.35;-0.16	**0.01**
Total errors^{log}	10.2 (0-79)	4.7 (0-70)	-0.48	-1.07;0.12	0.11
Spatial Span:					
Span length	6.4 (1.3)	7.0 (1.4)	-0.31	-0.90;0.28	0.31
Processing speed			-1.45	-2.08;-0.81	**<0.0001**
Verbal Fluency[a]					
Letters	19.4 (7.0)	30.3 (8.3)	-1.25	-1.84;-0.65	**<0.0001**
Categories	39.8 (9.9)	55.5 (12.3)	-1.21	-1.81;-0.61	**<0.0001**

Trail Making Test[a]					
Trail Making A[log], *s*	31.5 (18.0-68.1)	25.2 (12.8-51.4)	-0.63	-1.22;-0.02	**0.04**
Trail Making B[log], *s*	73.5 (40.9-169.2)	52.2 (31.2-131.1)	-0.66	-1.26;-0.07	**0.02**
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	58.7 (9.0)	-1.09	-1.68;-0.49	**0.0003**
Visuospatial memory			-0.74	-1.32;-0.05	**0.02**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.0 (4.3)	-0.67	-1.26;-0.08	**0.03**
Delayed recall, *score*	23.8 (5.0)	28.0 (4.4)	-0.83	-1.42;-0.24	**0.006**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.93 (0.1)	-0.70	-1.30;-0.11	**0.01**
Reaction time			-1.48	-2.10;-0.85	**<0.0001**
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9-988.6)	330.0 (247.6-464.1)	-1.81	-2.40;-1.22	**<0.0001**
Movement, *ms*	417.8 (86.3)	338.3 (80.1)	-0.84	-1.43;-0.25	**0.006**

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis.

Clinical characteristics at follow-up

In spite of several invitations to attend a follow-up examination two patients dropped out from baseline to follow-up. Clinical characteristics and baseline test-scores in these 2 patients did not differ from the rest of the patient group.

Twenty-nine patients were reexamined at the 3-month follow-up. One patient refused to have lumbar puncture performed at follow-up. A normalized ICP was found in 14 of the remaining 28 patients. Less than half of the patients had headache during cognitive re-testing (Table 1). Visual fields were either stable or had improved from baseline.

Fourteen of 31 patients had resumed work/school, 11 patients were now on long-term sick-leave, one patient had reduced and altered work schedule due to IIH, two patients were unemployed.

Cognitive function at follow-up

After 3-months of treatment statistical significant improvement was detected in two domains (Table 3). Attention scores (RVP A') had practically normalized while performance in visouspatial memory tests improved to a level above performance in healthy controls.

No overall change was detected in the domains of executive function, working memory, processing speed and reaction time (Figure 2). Patients in which ICP had normalized (<25 cmH_2O) did not perform better than patients in which elevated ICP persisted (ICP>25 cmH_2O) and performance was not significantly associated with intensity or presence/absence of headache during the test.

Table 3. Cognitive test scores and composite domain scores at follow-up compared to baseline

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	IIH Follow-up			
	n=31	n=29	Z[b]	95% CL	p
Executive function			-0.18	-0.77;0.42	0.16
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors[log]	8.1 (0–32)	5.8 (1–32)	-0.82	-1.40;-0.25	0.77
Total errors adjusted[log],	20.9 (7–177)	14.4 (7–68)	-0.56	-1.14;0.01	0.26
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	19.9 (2.0)	-0.08	-0.66;0.49	0.55
Initial thinking time[log], *s*	6.5 (2.0–18.3)	6.7 (2.5–18.4)	0.45	-0.14;1.02	0.98
Subsequent thinking time[log], *s*	0.013 (0–3.7)	0.013 (0–3.7)	0.11	-0.47;0.68	0.85
Trail Making Test[a]					
Trail Making B-A[log], *s*	39.2 (14.7–101.1)	33.1 (1.3–79.5)	0.46	-0.12;1.05	**0.002**
Working memory			-0.33	-0.84;0.18	0.44
Spatial Working Memory					
Strategy score[log]	29.9 (20-42)	27.9 (19–42)	-0.24	-0.81;0.34	0.10
Total errors[log]	10.2 (0–79)	10.1 (0–61)	-0.24	-0.81;0.34	0.50
Spatial Span:					
Span length	6.4 (1.3)	6.4 (1.3)	-0.27	-0.85;0.31	0.96
Processing speed			-1.23	-1.83;-0.64	0.49
Verbal Fluency[a]					
Letters	19.4 (7.0)	18.6 (6.6)	-1.27	-1.86;-0.69	0.88
Categories	39.8 (9.9)	42.5 (10.8)	-0.93	-1.51;-0.34	0.41
Trail Making Test[a]					

Trail Making A[log], *s*	31.5 (18.0–68.1)	32.9 (9.8)	-0.56	-1.15;0.02	0.95
Trail Making B[log], *s*	73.5 (40.9–169.2)	66.1 (38.7–125.4)	-0.18	-0.79;0.40	0.16
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	49.1 (12.3)	-0.91	-1.49;-0.33	0.50
Visuospatial memory			0.39	-0.17;1.02	**0.0005**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.9 (4.1)	0.36	-0.22;0.93	**0.002**
Delayed recall, *score*	23.8 (5.0)	28.8 (3.8)	0.31	-0.26;0.89	**0.0002**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.92 (0.04)	-0.14	-0.71;0.43	**0.03**
Reaction time			-1.31	-1.90;-0.71	0.90
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9–988.6)	387.4 (393.0–710.1)	-1.45	-2.02;-0.88	0.68
Movement, *ms*	417.8 (86.3)	412.3 (72.1)	-0.89	-1.46;-0.31	0.32

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis. Z[b]: Patients at follow-up compared to healthy controls.

DISCUSSION

This study is the first to comprehensively explore the cognitive functions in a cohort of more than 10 patients with IIH. We examined 31 patients and found moderate to severe deficits in four of six cognitive domains suggesting that IIH is associated with a global cognitive dysfunction.

Cognitive function in IIH has only been reported in three studies[5-7] in addition to a single case-report[8]. One study[6] examined 85 patients but applied only a single memory test and the methodology was not described in details.. The remaining studies performed more extensive cognitive testing, but in contrast to our study were uncontrolled and included only respectively one, five and 10 patients[5;7;8] Prior studies were, in addition, based on patients with a wide range of disease duration (6-98 months) and only one study[5] reported ICP at time of testing. Our study is the first to assessed the cognitive function in a well-defined group of patients with newly diagnosed disease (n=29) or relapse (n=2).

While the case-study of Kaplan et al.[8] found no convincing cognitive deficits, Arseni et al.[6] and Kharkar et al.[7] reported substantial deficits in memory. We found deficits in visuospatial memory and in spatial working memory strategy, but detected no overall difference in working memory. Verbal memory (measured by Wecheler Memory Scale) was by far the most affected parameter in the study of Kharkar et al. and similarly was reported moderate to severe in 90% of the patients studied by Arseni et al. Although we did not test verbal memory we found significant deficits in other verbal functions (verbal fluency). This is in line with the study of Sorensen et al.[5] reporting verbal deficits in all of their five patients. Deficits in phonological fluency, which were substantial in our patients, have been shown to relate to frontal lobe damage, reflecting an additional executive component.[14]

The most severe deficits in our study were found in the domains of reaction time and processing speed which is consistent with the study of Sorensen et al.[5] In addition we found significant

impairment in cognitive flexibility. Cognitive flexibility is fundamental for effective decision-making and the ability to learn and adapt to environmental changes, but has never been tested in patients with IIH before.

Although overall working memory was not affected in our study, patients did score significantly worse in the working memory strategy. This may reflect an executive component consistent with other executive deficits detected in our patients.

The deficits we detected in the domains of reaction time, processing speed, visuospatial memory and attention were equivalent to those found in patients with first episode schizophrenia.[15] In addition deficits in cognitive flexibility were similar to those (measured by Wisconsin Card Sort, a task conceptionally akin to the Intra-Extra Dimensional Set Shift Test) found in a meta-analyses of patients with schizophrenia in general.[16] Verbal fluency in our patients was affected to the same extents as reported for patients with schizophrenia[16] as well as patients with congentital hydrocephalus.[14] Furthermore deficits in verbal phonological fluency and processing speed (measured by Symbol Digit Modalities Test) were in the range found in patients with multiple sclerosis.[17-19]

Despite marked improvement in ICP and headache we found no convincing signs of overall cognitive improvement at the 3- month follow-up and the improvement seen in the visuospatial tests could be explained by learning effect (familiarization with the Rey Ostereith Complex Figure). Sorensen et al.[5] reported that although signs of cognitive dysfunction were only minor, four of their five patients were unable to manage work and/or everyday activities. In our study 12 of the 31 patients were either on long-term sick-leave or had reduced and altered work schedule due to IIH at follow up three months after diagnosis. Short follow-up and co-existent headache-symptoms limit the interpretation of the socioeconomic impact of cognitive dysfunction demonstrated in our study. However, in other well recognized diseases such as schizophrenia a robust relationship between

global and specific cognitive deficits and functional outcome has been consistently demonstrated.[20;21]

The cause of cognitive impairment in IIH remains speculative. Theories could involve dysfunction of grey and/or white matter substance due to mechanical compression as proposed in normal pressure hydrocephalus,[14] dysfunction related to axonal flow as in optic nerve swelling and dysfunction[22] or release of cytotoxic substances as is seen in other conditions with cognitive decline.[23] However, the pathophysiology of IIH and the related changes in cerebral tissue composition is still largely unknown. Diffuse cerebral edema has been suggested by some[24;25] but refused by others.[26;27] Thus further studies of morphological changes in cerebral structure and composition that could explain the cognitive impairment demonstrated in this study would be of great interest.

The strengths of the study is the prospective and controlled design, the broad range of cognitive tests, a relatively large study population, and the use of a culturally blind and computerized test battery that by automatic test conduction and score recording reduced the influence of the non-blinded observer. In addition the study population was well defined with cognitive testing performed in close relation to IIH diagnosis and ICP measurement. As patients were enrolled consecutively from both neurological and ophthalmological departments our study population reflects representative IIH-patients and not a selected group of cognitively symptomatic patients.

The study was limited by the non-blinded design, the relatively short follow-up period and the lacking re-test of healthy controls. In addition controls were not matched for weight or headache. Applying patients with chronic primary headache as controls could be advocated. However, although cognitive impairment in other headache disorders such as migraine has been debated,[28-30] a recent comprehensive review concluded that there is no evidence of cognitive dysfunction in patients with migraine.[31] Cognitive outcome was adjusted for headache at time of testing, but we were unable to in addition adjust for BMI as obesity was strongly correlated to being in the patient group. Obesity

alone has been associated with cognitive deficits. [32] However, obesity is primarily is associated with deficits in the executive area in contrast to the pattern of deficits found in our patients.

In conclusions, this study strongly suggests that IIH is a disabling neurological disorder associated with moderate to severe cognitive deficits. The results in addition indicate that the cognitive deficits are long-lasting, not paralleling ICP and headache reduction, and are not sufficiently treated by diuretics and weight loss. Contrary to our hypothesis executive and memory functions were only moderately affected. Nevertheless we found substantial deficits in processing speed and reaction time which could explain some of the severe difficulties that patients encounter in work and daily activities. A focused multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with IIH.

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COMPETING INTERESTS

H. Yri has received honoraria for consultant work from Neurocore and a travel grant from Berlin-Chemi Menarini. B. Fagerlund and H. Forchhammer report no disclosures. R. Jensen has received honoraria for lectures and patient leaflets from MSD, Berlin-Chemie Menarini, ATI and Pfizer and serves on medical advisory boards for LindeGas, ATI and Neurocore.

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AUTHOR CONTRIBUTION

HMY made a substantive intellectual contribute to the design of the study, acquistion, analysis and interpretation of the data, and the drafting and revision of the manuscript.

BF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

HBF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

RHJ made a substantive intellectual contribute to the conceptualization and design of the study, the interpretation of the data and the revision of the manuscript.

DATA SHARING STATEMENT

No additional data are available

EXCLUSIVE LICENCE

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FIGURE TITLES AND LEGENDS

Figur 1.

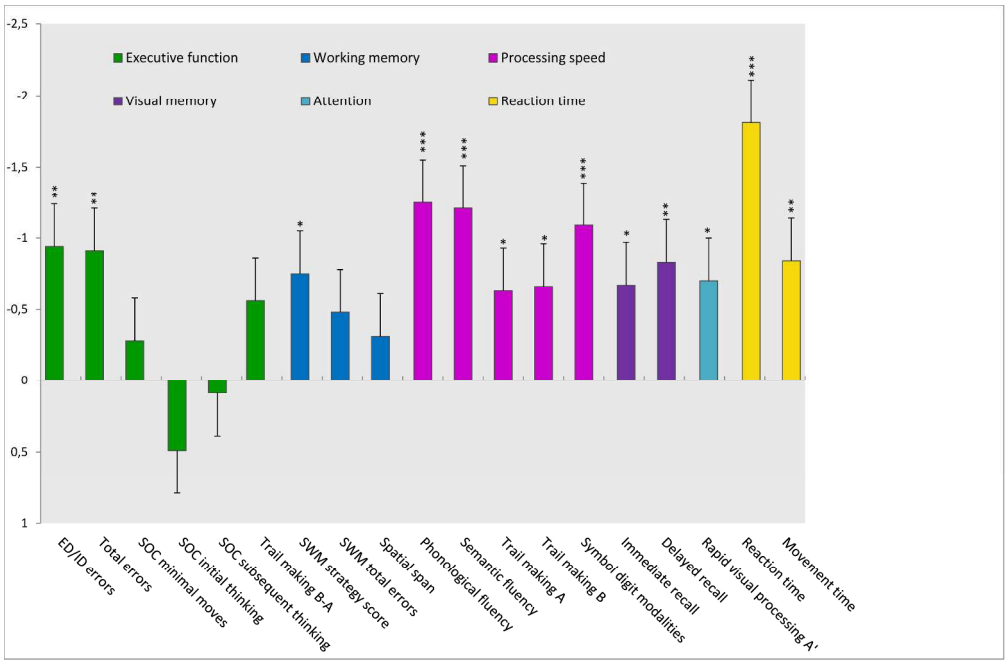
Title: Cognitive deficits in patients with IIH at time of diagnosis

Legends: Cognitive function in patients with IIH at time of diagnosis (n=31) shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. Colors indicate which domain the tests represent. *p<0.05 **p<0.005 ***p<0.0005.

Figure 2.

Title: Cognitive deficits in patients with IIH at time of diagnosis and at follow-up

Legends: Changes in test performance from time of diagnosis to follow-up (n=29) in patients with IIH shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. *p<0.05 **p<0.005 ***p<0.001.



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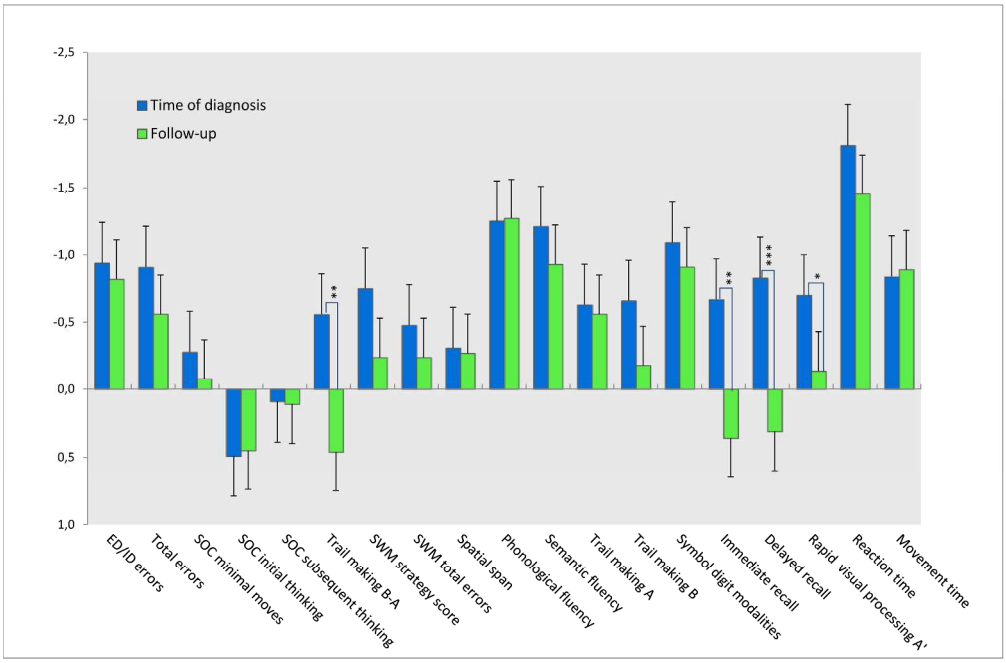

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls page 4-5
		(*b*) For matched studies, give matching criteria and the number of controls per case page 4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6-7
Bias	9	Describe any efforts to address potential sources of bias page 7-8
Study size	10	Explain how the study size was arrived at page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions page 7-8
		(*c*) Explain how missing data were addressed page 7-8
		(*d*) If applicable, explain how matching of cases and controls was addressed page 5
		(*e*) Describe any sensitivity analyses not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10,14,15
		(b) Give reasons for non-participation at each stage page14
		(c) Consider use of a flow diagram not applied
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10-11
		(b) Indicate number of participants with missing data for each variable of interest page 11,13,16
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure page 10,14,15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10-16
		(*b*) Report category boundaries when continuous variables were categorized page 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 14
Discussion		
Key results	18	Summarise key results with reference to study objectives page 17-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 20
Generalisability	21	Discuss the generalisability (external validity) of the study results page 18-20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 21

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

18-02-2011

Protokol

Idiopatisk intrakraniel hypertension – neurobiologiske og neuropsykologiske aspekter

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18-02-2011

Indholdsfortegnelse

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3. Projektdeltagere.
4. Baggrund.
5. Formål.
6. Patientmateriale.
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8. Effektmål
9. Statistik
10. Rissici, bivirkninger og ulemper
11. Etiske overvejelser
12. Tidsplan.
13. Publikation.
14. Økonomi.
15. Initiativtagere
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Bilag.

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   - 7b. 15-17 årige
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10. Flowchart

10a: del I-III

10b: del IV

1. Titel

Titel

Idiopatisk intrakraniel hypertension – neurobiologiske og neuropsykologiske aspekter

1.2 beskrivende titel

Longitudinel prospektiv undersøgelse af neurobiologiske og neuropsykologiske forhold hos patienter med idiopatisk intrakraniel hypertension.

2. Sted for undersøgelsen

Dansk Hovedpinecenter, neurologisk afdeling og Øjenafdelingen Glostrup Hospital, 2600 Glostrup.

3. Projektdeltagere

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4. Baggrund

Idiopatisk intrakraniel hypertension er en lidelse kendetegnet ved forhøjet intrakranielt tryk uden kendt til grundliggende årsag. Diagnosen forudsætter at andre kendte årsager til trykforhøjelsen er udelukket ved grundig radiologisk, serologisk og klinisk udredning. Klinisk er tilstanden kendetegnet ved symptomer i form af en svær hovedpine, synsforstyrrelser i form af transitoriske

visuelle obskurationer (TVO) og dobbeltsyn, samt pulserende tinnitus [9,18]. Objektivt manifesterer lidelsen sig i de fleste tilfælde med bilateralt papilødem som følge af trykforhøjelsen. Nogle patienter udvikler af ukendte årsager aldrig papilødem ligesom unilaterale eller asymmetriske ødemer også forekommer [14]. Udover eventuel abducens parese må der definitionsmæssigt ikke foreligge andre neurologiske udfald [1, 6].

Lidelsen rammer typisk overvægtige kvinder i fødedygtig alder. Incidensen i denne gruppe skønnes ud fra epidemiologiske studier at være ca. 20 per 100.000 hvilket er 20 gange højere end for normalbefolkningen [4, 15, 16]. I takt med den aktuelle fedme epidemi verden over må forekomsten af IIH og dens relaterede morbiditet i gruppen af yngre overvægtige kvinder forventes at være stadig stigende. På trods af den endnu relative lave forekomst skønnes de socioøkonomiske konsekvenser af sygdommen at være betydelige [8].

De væsentligste komplikationer til forhøjet intrakranielt tryk er risikoen for progredierende og varigt synstab samt kronisk hovedpine. Hovedpine ses hos ca. 90 % i det initielle akutte forløb af IIH og hos mange patienter persisterer den som en kronisk invaliderende hovedpine også efter at det intrakranielle tryk er normaliseret [7].

IIH hovedpinens karakteristika er ikke entydige og kan i sine manifestationer ligne såvel migræne som andre primære hovedpineformer. I det Internationale Hovedpineselskab's Klassifikation(ICHD-II) af IIH forudsættes at hovedpinen aftager ved normalisering af trykket og forsvinder inden for 72 timer ved opretholdelse af normalt tryk [1]. Dette er dog i praksis et vanskeligt anvendeligt kriterium, der primært er bygget på en klinisk observation, idet trykmålingerne er invasive og sjældent kontinuerlige. Kriterierne er imidlertid aldrig blevet systematisk evalueret.

Patogenesen bag hovedpinens kronificering er ukendt, men en øget aktivering (ekscitation) af områder i centralnervesystemet der har med smertebehandling at gøre (central sensibilisering) kan tænkes at være involveret.

Central sensibilisering manifesterer sig bl.a. ved allodyni (smerte ved ikke-smertefulde stimuli) og hyperalgesi (øget respons pa smertestimuli) som vha. Quantitative Sensory Testing (QST) kan måles som hhv. nedsatte smertetærskler og øget smerteføl somhed for stimuli over tærskelniveau (Supra Threshold Score).

Synstabet ved forhøjet intrakranielt tryk er i de fleste tilfælde langsomt progredierende og kan initielt være asymptomatisk idet det centrale synsfelt typisk først påvirkes sent i forløbet. Ved

længerevarende ødem og trykpåvirkning indskrænkes synsfeltet efterhånden som atrofien tiltager. En ældre, større prospektiv undersøgelse af 50 IIH patienter påviste blivende synsdefekter hos knap halvdelen af patienterne, mens 5 % -10 % af patienterne blev blinde på et eller begge øjne [27].
I tillæg til tidligere nævnte klassiske symptomer ved IIH synsforstyrrelser, hovedpine, pulserende tinnitus) synes tilstanden i høj grad at være associeret med kognitiv og psykisk påvirkning. På trods af at IIH patienterne hyppigt klager over kognitive symptomer er de reelle deficits kun sparsomt undersøgt. Et studie af 85 patienter som udelukkende testede hukommelse rapporterede fandt en påvirkning hos 24 % af patienterne [2]. En anden og mindre undersøgelse tyder på at de kognitive deficits er reversible ved normalisering af trykket [24].
Depression- og angstsymptomer forekommer også hyppigt hos IIH [11, 12] også uden forudgående psykisk sygdom og påvirker i kombination med de fysiske gener patienternes livskvalitet og funktionsniveau. Da depression og angst ifølge flere tidligere studier kan påvirke patienternes præsentation ved neuropsykologiske test [5, 10, 17, 26] er det vigtigt at kontrollere herfor disse ved undersøgelse af de kognitive test.

Vægttab er udover medicinsk behandling og i hurtigt progredierende tilfælde kirurgisk intervention den primært anbefalede behandling. Flere studier har vist positiv effekt på forløb og nedsat behov for medicinsk behandling efter selv mindre vægttab [13, 23, 27, 28]. Et helt nyt prospektivt studie på 25 patienter viste klar signifikant reduktion i ICP samt bedring af symptomer og papilødem efter lav energi diæt og vægttab [20].

Der foreligger endnu ikke tilfredsstillende forklaring på den patogenetiske kobling mellem overvægt og IIH. Såvel simpel mekanisk kompression af central fordelt fedtvæv medførende intraabdominal og sidenhen intrakraniel venøs trykforhøjelse som mere kompleks neuroendokrin dysfunktion har været foreslået [3, 19, 25]. F.eks. er ekspressionen af det cortisol dannende enzym 11ß-HSD1 som indgår i homeostasen og reguleringen af det intraokulære tryk og på lignende vis tænkes at have en rolle i CSF regulationen, forhøjet i fedtvæv [19, 21]. I et nyligt studie er det vist at ekspressionen af dette enzym falder ved vægttab hos IIH patienter. Faldet i enzymaktivitet korrelerede endvidere med symptombedring og demonstreret fald i ICP. [21]
Andre vægtrelaterede og mulige regulatorer af ICP homeostasen er de natriuretiske peptider. En af undertyperne C-type natriuretisk peptid (CNP) der har kendt vasodilaterende virkning har et tæt koncentration af receptorer på plexus choroideus hvor to tredjedele af CSF produceres.

Kombinationen af en nedsat plasmakoncentration af Pro-CNP hos IIH patienter og en stigning af samme i relation til vægttab og symptombedring er netop fundet i Maren Skau's studie fra Dansk Hovedpinecenter [22] og en vægtrelateret dysregulation af kartonus er foreslået involveret i patogenesen bag IIH.

Livstilsændring og vedligehold af opnået vægttab synes at være den største udfordring i overvægtsproblematikken. I en nylig opfølgningsundersøgelse af en gruppe IIH- patienter fra DHC havde kun 24 % opnået et vedvarende vægttab (≥ 5 %), mens næsten halvdelen af patienterne (48 %) ligefrem havde taget på efter diagnosetidspunktet på trods af diætistforløb og udtrykkelig information om den latente risiko for permanente synsdeficit [29].

5. Formål

Formålet med studiet er at belyse oftalmologiske, kliniske og neuropsykologiske aspekter af IIH

Del I. Formål: at karakterisere den initielle IIH hovedpine og evaluere de eksisterende diagnostiske kriterier

Del II. Formål: at undersøge en eventuel påvirkning af den kognitive funktion ved IIH samt ændring i relation til behandling.

Del III. Formål: at identificere og undersøge mulige biomarkører for IIH

Del IV. Formål: at undersøge den prognostiske effekt af et IIH-skoleforløb

6. Forsøgspersoner

Patienter vil blive rekrutterede fra Dansk Hovedpine Center, neurologisk, neurokirurgisk samt oftalmologisk afdeling, Glostrup Hospital. Der vil ligeledes blive rettet henvendelse til landets øvrige neurologiske, neurokirurgiske og oftalmologiske afdelinger med henblik på rekruttering af patienter samt ved opslag på diverse opslagstavler og afdelingernes hjemmesider (se annonce).

Raske kontroller til del II vil blive rekrutteret fra Dansk Hovedpine Center, mens der til del III vil blive anvendt et allerede indsamlet materiale [22] (protokol journalnummer H-KA 20070003). Undersøgelse af kontroller til del II omfatter udelukkende de kognitive funktioner som beskrevet under punktet nedenfor.

Del I: 25 IIH-patienter

Inklusionskriterier:

Alder mellem 15 til 65 år

IIH i henhold til det Internationale Hovedpine Selskabs klassifikationskriterier (ICHD- II)

Anden intrakraniel patologi er udelukket med CT- angio eller MR venografi

Eksklusionskriterier:

Andre alvorlige somatiske sygdomme

Alvorlig psykisk sygdom

Kronisk hovedpine af andre årsager

Analgetikaoverforbrug iht. ICHD-II

Profylaktisk behandling mod hovedpine

Utilstrækkelige dansk-kundskaber

Del II: 25 IIH-patienter og 25 raske kontroller

Inklusionskriterier for patienter:

Alder mellem 15 til 65 år

ICP > 25 cm H_2O

IIH i henhold til det Internationale Hovedpine Selskabs klassifikationskriterier (ICHD- II)

Anden intrakraniel patologi er udelukket med CT- angio eller MR venografi

Inklusionskriterier for kontroller:

Alder mellem 15 til 60 år

18-02-2011

Primær hovedpine

Eksklusionskriterier for patienter og kontroller

Andre alvorlige somatiske sygdomme

Alvorlig psykisk sygdom

Kendte kognitive deficit eller sygdomme/ tilstande der påvirker den kognitive funktion

Behandling med medikamenter hvor kognitiv påvirkning er sandsynlig

Utilstrækkelige dansk-kundskaber

Del III: 25 IIH-patienter samt tidligere indhentede blodprøve- og spinalvæskeprøver fra 20 raske overvægtige kontroller

Inklusionskriterier:

Alder mellem 15 til 65 år

IIH i henhold til det Internationale Hovedpine Selskabs klassifikationskriterier (ICHD- II)

Anden intrakraniel patologi er udelukket med CT- angio eller MR venografi

ICP > 25 cm H_2O

Eksklusionskriterier:

Andre alvorlige somatiske sygdomme

Kendte hjertelidelse

Utilstrækkelige dansk-kundskaber

Del IV: 25 IIH-patienter

Inklusionskriterier:

Alder mellem 15 til 65 år

ICP > 25 cm H_2O

IIH i henhold til det Internationale Hovedpine Selskabs klassifikationskriterier (ICHD- II)

Anden intrakraniel patologi er udelukket med CT- angio eller MR venografi

Eksklusionskriterier:

Andre alvorlige somatiske sygdomme

Alvorlig psykisk sygdom

Kronisk hovedpine af andre årsager

Analgetika overforbrug iht. ICHD-II

Utilstrækkelige dansk-kundskaber

7. Metode

For oversigt over undersøgelser se flowchart (bilag)

Generel klinisk undersøgelse

En komplet journaloptagelse, inklusiv detaljeret interviewskema (se bilag 2a), samt neurologisk og somatisk undersøgelse vil blive foretaget på alle IIH-patienter ved diagnose eller inklusions-tidspunkt. Demografiske data (højde, vægt, liv- og hoftemål) bestemmes for samtlige forsøgsdeltagere, lige såvel som kardiovaskulær sygdom udelukkes ved BT-måling og EKG. Lumbalpunktur med registering af åbningstryk samt tapning af cerebrospinalvæske til såvel biokemisk undersøgelse som opnåelse af et normaliseret sluttryk foretages ved inklusion samt efter 3 måneders behandling. Ved opfølgende kontroller er 30, 60 og 90 dage gentages det strukturerede interview i en forkortet udgave (bilag 2b)

Generel oftalmologisk undersøgelse

Synsstyrke (visus): ETDRS og Snellen

Farvesyn (Ishihara), pupilrefleks, motilitets- og diplopivurdering, spaltelampeundersøgelse, intraokulær trykmåling (Goldmann) og indirekte oftalmoskopi i medicinsk mydriasis.

Synsfeltsundersøgelse: Automatiseret perimetri (Humphrey Static Perimetry 30-2)

Fundus-foto

Optical coherence tomography (peripapillært samt makulært med sfærisk korrektion) med måling af RNFL og RT

Ovennævnte undersøgelser foretages ved inklusion samt efter 1 og 3 mdr. Den kliniske del foretages af neurooftalmolog MW

Diamox og evt. Furix behandling vil blive seponeret 72 timer forud for Oftalmologisk undersøgelse samt trykmåling. For Topimax er seponeringsperioden 7 døgn.

Hovedpinekarakteristika (del I)

Patienter vil blive bedt om at føre en detaljeret hovedpine/symptomdagbog (se bilag 3) den 1. måned efter diagnosticering/inklusion. Derefter overgår patienterne til en mindre omfattende registrering ved en hovedpine/symptom kalender (se bilag 4).

Til vurdering af central sensibilisering vil patienterne blive undersøgt ved Quantitative Sensory Testing. Metoden bestemmer smertetærskler samt Supra Treshold Score vha. trykalgometer, palpometer, og elektrisk stimulation.

Kognitiv vurdering (del II)

Den kognitive funktion undersøges dels ved et batteri sammensat af neuropsykologiske test som måler forsøgsdeltagerens evne til at løse en række opgaver der afspejler den globale kognitive funktion. Undersøgelsesprogrammet vil bestå af dels computeriserede test (CANTAB) og dels tests på papirform. Som supplement til den kognitive testning fortages efterfølgende supplerende test og spørgeskemaer til vurdering af symptomer på depression og angst, livskvalitet og præmorbidt funktionsniveau.

Ovennævnte undersøgelses program foretages hos IIH patienter på diagnosetidspunktet snarest muligt efter opstart af relevant behandling og gentages efter 3 mdrs. behandling. Raske kontrolpersoner undersøges ved en enkelt anledning. Intensiteten af eventuel hovedpine på forsøgsdagen noteres.

IIH patienter vil som led i den generelle udredning af sygdommen få foretaget en voxel morfometrisk MR scanning. Disse scanningsfund vil blive vurderet mhp. differentialdiagnoser og en eventuel association mellem synlige substans forandringer og kognitiv påvirkning.

Biomarkører (del III)

Faste-blodprøver ved inklusion samt efter 1 og 3 mdr.: glukose, HbA1c, lipider, total Kolesterol, Kolesterolfraktioner, Na, K, kreatinin, Hb. ANP, BNP, CNP samt pro-ANP, Pro-BNP og pro-CNP, angiotensin, cytokiner, cholecystokinin, leptin, grehlin, og relaterede peptider.
Cerebrospinalvæske (tappes i forbindelse med trykmåling) ved inklusion og efter 3 mdr.: celler, glukose, protein, IgG-index, ANP, BNP, CNP, pro-ANP, Pro-BNP og pro-CNP, angiotensin, glukose, HbA1c, lipider, total kolesterol, kolesterolfraktioner, cytokiner, cholecystokinin, leptin, grehlin, og relaterede peptider.

IIH-skole (del IV)

Forsøgspersoner med IIH inkluderet i del I-III vil i forlængelse af disse studier blive tilbudt at indgå i del IV. I dette studie blok-randomiseres forsøgspersonerne i blokke á 6 stk. til a) et IIH-skole forløb og b) almindeligt opfølgningsforløb
IIH-skoleforløbet består af et forløb over 12 uger med 6 sessioner bestående af a) individuel undersøgelse og vejledning, b) undervisning i grupper og c) samtalegrupper.
Undervisning, vejledning og undersøgelse forestås af diætist, fysioterapeut, psykolog, sygeplejerske/sosu-assistent og forsøgsansvarlige læge. Efter afsluttet forløb følges patienterne med besøg efter 6 og 12 mdr.
Samtlige forsøgspersoner får foretaget:
Detaljeret øjenundersøgelse (ovenfor beskrevet): ved opstart samt efter1, 3, 6 og 12 mdr.
Objektiv undersøgelse i form af vægt, talje- og hoftemål, kondital, blodtryk, blodprøver med plasma værdier af kolesterol, lipider og BS foretages ved opstart, efter 1, 2,3, 6 og 12 mdr.
Struktureret interviewskema i den forkortede udgave (bilag 2b) med henblik på symptomer og medicinsk behandling samt spørgeskema til selvvurderet livskvalitet udfyldes ved opstart samt efter 1, 3, 6 og 12 mdr.

8. Effektmål

Primære effektmål

Del I

At karakterisere Hovedpinen og forløbet af denne de første 3 måneder efter debut af IIH.
At validere de eksisterende diagnostiske ICHD-II kriterier for IIH

Del II

At undersøge forekomsten af kognitive deficits hos IIH patienter samt effekten af behandling på denne.

Del III

Forskel i plasma-koncentrationen af appetit-regulerende hormoner mellem IIH-patienter og raske, vægt korrelerede kontroller.

Forskel i cerebrospinalvæskens koncentrationen af appetit-regulerende hormoner mellem IIH-patienter og raske, vægt korrelerede kontroller.

Forskellen i plasma- og csf-koncentrationen af pro-ANP, pro-BNP og pro-CNP mellem IIH-patienter og vægt-korrelerede raske kontroller før vægttab.

Forskellen i plasma- og csf-koncentrationen af pro-ANP, pro-BNP og pro-CNP hos IIH-patienter før og efter vægttab.

Forskel i plasma- og cerebrospinalvæskekoncentration af cytokiner, lipid og cholesterol mellem IIH-patienter og raske, vægt korrelerede kontroller.

Del IV

At undersøge effekten af et IIH-skoleforløb på outcomeparametre i form af vægt, synsfunktion, hovedpine, medicineringsbehov og livskvalitet

Sekundære effektmål:

Del I:

At undersøge for tegn på central sensibilisering ved IIH hovedpine.

Del II

At undersøge for fund af strukturelle ændringer på IIH-patienters diagnostiske MR scanning med evt. kognitive defekter. At beskrive forskelle i selvvurderet livskvalitet, angst og depressionssymptomer mellem IIH-patienter og andre patienter med kroniske hovedpine.

9. Statistik

Parametrisk og non-parametrisk statistik vil blive brugt afhængigt af, om data er normalfordelt. Forskelle i effektparametre mellem patienter og kontroller vil blive testet med uparret statistik.

Forskelle i effektparametre hos patienter ved start og under followup vil blive testet med parret statistik. Der benyttes signifikansniveau 5 %.

Beregning af nødvendigt antal forsøgspersoner:

Der accepteres en risiko for type 1 fejl på 5 % og en risiko for type 2 fejl på 20 % (dvs. power 80 %). En decideret power beregning er ikke mulig grundet det begrænsede kendskab til de planlagte effektparametres størrelse og varians. Dropout ved studierne I-III forventes at være relativ lav (cirka 10 %), eftersom undersøgelserne kan gennemføres i forbindelse med opfølgning på Hovedpine Centeret og på Øjenafdelingen. Pga. symptomer og risikoen for udvikling af varige synsdefekter er patienterne generelt motiverede for opfølgning de første måneder. Dropout ved studie IV forventes noget højere (ca. 20 %) pga. det længere forløb. Det nødvendige antal af forsøgspersoner vurderes at være 25 personer.

10. Rissici, bivirkningerog ulemper

10.1. Vedrørende undersøgelsen som helhed

De planlagte undersøgelser er kendte og anvendes i forvejen som led i klinisk udredning og behandlingskontrol og det skønnes derfor ikke at medføre unødig ulempe og risici for patienterne.

10.2. Vedrørende øjenundersøgelserne

De oftalmologiske undersøgelser er alle i forvejen kendte og anvendte undersøgelser i klinikken hos andre patientgrupper. De er atraumatiske og udgør ikke nogen risiko eller noget nævneværdigt ubehag. De anvendte mydriatika (mydriacyl, metaoxedrin) er alment anvendte i klinikken. Velkendte bivirkninger er kortvarig akkomodationsbesvær og lysskyhed. Dråberne er kontraindicerede ved snævervinklet glaukom. Glaukom og svær refraktionsanomali er eksklusionskriterier i undersøgelsen.

10.3. Vedrørende laboratorieundersøgelserne

Blodprøvetagning udgør ikke nogen risiko eller noget nævneværdigt ubehag.

Lumbalpunktur indgår som en vanlig diagnostisk undersøgelse som er påkrævet for at stille diagnosen uanset om patienten indgår i projektet eller ej. Risikoen for infektion ved lumbalpunktur er yderst minimal. Indgrebet vil blive foretaget ved aseptisk teknik. En eventuel infektion vil blive behandlet med antibiotika. Risikoen for postlumbal lavtrykshovedpine er 5-7 % og kan behandles konservativt med sengeleje og væske samt eventuelt med blood patch. Let smerte må forventes.

10.4. Vedrørende undersøgelse for central sensibilisering

Undersøgelsen udgør ikke nogen risiko for forsøgspersonen. Den langsomme stigning i stimulusstyrke sikrer, at kun moderat smerte påføres.
Vi har stor erfaring med disse smertemålinger og de har aldrig givet anledning til uhensigtsmæssigt ubehag.

10.5. Vedrørende den kognitive testning

Den kognitive testning samt den tilknyttede MR scanning udgør ikke nogen risiko eller ubehag for patienten.

11. Etiske overvejelser

11.1. Vedrørende projektet som helhed

Denne patientgruppe repræsenterer en relativ sjælden sygdom, der dog er i hastig stigning på grund af fedmeepidemien og sygdomsmekanismen kendes kun sparsomt. I betragtning af sygdommens betydelige invaliditetsgrad, den unge aldersgruppe, store risiko for blindhed og de ringe behandlingsmuligheder vil en systematisk undersøgelse af denne patientgruppe være af meget stor betydning og dermed til fulde opveje de minimale ulemper og risici, der er ved den aktuelle undersøgelse

11.2. Etiske overvejelser vedrørende data

Personidentificerbare data vil blive anonymiseret og behandlet i hht. Datatilsynets regler. Studiet vil blive anmeldt til datatilsynet.

11.3. Etiske overvejelser vedrørende biologisk materiale

Da ikke alle analyser udføres i umiddelbart tilslutning til udtagelse samt da der ønskes mulighed for yderligere analyser ved opståen af ny viden oprettes en forskningsbiobank. Henholdsvis 10 ml spinalvæske og 10 ml veneblod opbevares efter centrifugering og afpippetering i fryser. Materiale opbevares i anonymiseret form 15 år hvorefter det destrueres. Forsøgsdeltagere kan dog til enhver tid ved tilkendegivelse heraf få sit materiale destrueret. Materialet vil ikke blive videregivet til andre. Ny forskning i det biologiske material kan kun ske efter tilladelse fra Videnskabs Etisk Komité

11.4. Etiske overvejelser vedrørende information

Deltagerne giver skriftligt tilsagn om deltagelse i undersøgelsen efter at have modtaget fyldestgørende skriftlig og mundtlig information om formål, metode, ulemper og risici ved undersøgelsen. Deltagelsen er frivillig og deltagerne kan til enhver tid trække sig ud af undersøgelsen, uden at det vil få konsekvenser for deres fremtidige udredning og behandling. Undersøgelserne forventes ikke at medføre ubehag. Det anses derfor for etisk forsvarligt at gennemføre denne undersøgelse. Undersøgelserne vil blive udført i overensstemmelse med Helsinkideklarationen, modificeret ved 42. verdenskongres i 2000.

12. Tidsplan

Delstudie I-III

01.04.2011 - 31.03.2012 Inklusion af forsøgspersoner. Indsamling af data.

01.04.2012 – 31.03.2013 Sammenskrivning af data til artikelform.

Delstudie IV

01.07.2011 - 30.07.2013 Inklusion af forsøgspersoner. Indsamling af data.

01.10.2013 - 28.02.2014 Sammenskrivning af data til artikelform.

18-02-2011

13. Publikationer

Såvel positive som negative resultater vil blive offentliggjort.

Tentative titler og aftalt forfatterrækkefølge:

1) Yri HM, Wegener M, Hamman S, Jensen R: Characterization of Idiopathic Intracranial Hypertension related headache and symptoms in the initial 3 months after diagnosis.
2) Yri HM, Jensen R: Evaluation of the ICHD-II Diagnostic criteria for Idiopathic Intracranial Hypertension
3) Yri HM, Forchammer H, Fagerlund B, Jensen R: Cognitive Impairment in Idiopathic Intracranial Hypertension
4) Yri HM, Wegener M, Hamman S, Gøtze JP, Jensen R: The role of regulatory peptides in IIH
5) Yri HM, Wegener M, Hamman s, Christensen J, Rasmussen U.B, R. Jensen: IIH Headache school: Therapeutic Effect and Clinical Outcome

14. Økonomi

Der er endnu ikke opnået midler til finiancering af undersøgelsen. Der ansøges om økonomisk støtte ved offentlige og private fondsmidler. Videnskabsetisk komité samt forsøgsdeltagere der aktuelt er i forsøget vil blive underrettet om beløb, udbetalingsmåde og navn på den enkelte støttegiver samt dennes forbindelse til projektansvarlige så snart øknomisk støtte til undersøgelsen foreligger. Forsøgspersoner vil blive tilbudt transportgodtgørelse svarende til billigste transportmulighed og modtager ikke anden godgørelse for deltagelse i undersøgelsen

.

15. Initiativtagere

Initiativ til projektet er taget af Hanne M. Yri og Rigmor Jensen

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Idiopathic intracranial hypertension is associated with cognitive dysfunction — a prospective case-control study

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Idiopathic intracranial hypertension is associated with cognitive dysfunction — a prospective case-control study

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Idiopathic intracranial hypertension, pseudotumor cerebri, cognition disorders, case-control studies.

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ABSTRACT

Objective: To explore the extent and nature of cognitive deficits in patients with idiopathic intracranial hypertension at time of diagnosis and after three months of treatment.

Design: Prospective case-control study.

Setting: Neurological department, ophthalmological department and a tertiary headache referral clinic at a Danish university hospital**.**

Participants: Thirty-one patients with definite idiopathic intracranial hypertension referred from June 2011– February 2013 and included within one week of diagnostic intracranial pressure measurement. Twenty-nine patients completed re-examined at the 3-month follow-up. At time of testing none of the patients took medication potentially affecting cognitive function. Controls were 31 healthy age- and sex-matched volunteers from the local community.

Outcome measures: Executive function, working memory, visuospatial memory, processing speed, attention, and reaction time assessed by a comprehensive neuropsychological test battery consisting of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB)) and paper-and-pencil tests.

Results: Patients with idiopathic intracranial hypertension performed significantly worse than controls in four of six cognitive domains ($p \leq 0.02$). Deficits were most pronounced in reaction time (1.45 SD below controls 95% CI 2.10 to 0.85) and processing speed (1.45 SD below controls 95% CI 2.08 to 0.81). Despite marked improvement in intracranial pressure and headache, re-examination showed persistent cognitive dysfunction three months after diagnosis and start of treatment.

Conclusions: We demonstrate for the first time in a well-defined cohort of patients that idiopathic intracranial hypertension may be associated with cognitive dysfunction. This could explain the functional disability of patients with idiopathic intracranial hypertension. A focused

multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with idiopathic intracranial hypertension.

ARTICLE SUMMARY

Strengths and limitations of this study

- The first study to assess a broad range of cognitive functions in more than 10 patients
- Prospective controlled design and a well defined study population
- Controls were matched for age, sex and pre-morbid intelligence and in comparisons of cognitive measures we adjusted for education and headache at time of testing.
- The study was non-blinded and controls were not matched for Body Mass Index (BMI)
- Cognitive assessment by an automated computerized test battery reduced the influence of the non-blinded observer

INTRODUCTION

Due to predilection for young individuals of working age idiopathic intracranial hypertension (IIH) is a condition with substantial socioeconomic consequences. In USA alone the estimated annual costs exceed $444 million (> $17,000 /patient).[1] In addition to direct medical cost the major expenses was loss of wages caused by patients having to give up work or change profession due to IIH. Loss of income due to IIH is reported by 48% of patients,[1] but the exact cause of this substantial disability is yet unknown.

Despite obvious threat to visual function compliance with long-term treatment is often poor. In our clinics we experience a substantial lack of initiative and self-awareness in patients with IIH which has raised the suspicion of prefrontal dysfunction. However, while numerous studies describe the visual and headache-related complications of IIH, very little is known about the cognitive implications of the disease. Except for a single memory test conducted in 85 patients[2] the cognitive function in IIH has only been tested in a few very small study populations.[3-5] In all studies, apart from the case-report by Kaplan et al.,[5] testing revealed significant cognitive deficits in patients with IIH. Especially within verbal tests and memory deficits have been demonstrated.

The aim of this case-control study is to explore in details the extent and nature of cognitive deficits in patients with IIH at time of diagnosis and after three months of treatment.

METHODS

Subjects

We recruited 31 consecutive patients with IIH referred to the Department of Neuro-Ophthalmology, the Department of Neurology or the Danish Headache Center, Glostrup Hospital from June 2011–February 2013. Sample size was determined by the number of cases referred in the inclusion period. Twenty-eight of the patients were newly diagnosed with IIH, three patients had well-defined relapse

of IIH after a minimum of 10 months (range 10-26 months) of medication-free remission (resolved headache and papilledema). All patients had definite IIH according to the diagnostic criteria.[6,7] We included only patients that could be tested within seven days of confirmed diagnosis. Exclusion criteria were: other disorders or medication that could potentially affect cognition, decreased visual aquity, or language skills (Danish) deemed insufficient for participation in the cognitive assessment. Thirty-one healthy and headache free (defined as less than 4 headache days/month) controls, matched for age and sex, were recruited by advertising at Glostrup Hospital and on the website forsogspersonen.dk. Healthy controls were tested only once and did not have a lumbar puncture performed. Otherwise the cognitive examination program for patients and controls was identical.

Standard protocol approvals, registration and patients consents

All participants gave written, informed consent to participate in the study. The study was conducted in accordance with the declaration of Helsinki and approved by the Regional Ethics Committee.

General examination

At time of diagnosis patients underwent a complete neurological examination including MR/CT-imaging with venous sequences. All but one patient underwent thorough standardized neuro-ophthalmological examination.[8] The remaining patient did not participate in the neuro-opthalmological evaluation in spite of numerous invitations. A general ophthalmological examination was, however, performed at the local referring ophthalmological department.

Treatment

After diagnostic lumbar puncture and after cognitive testing was completed, treatment with acetazolamide was initiated. From baseline to 3-month follow-up doses were individually adjusted at doses of 750-2225 mg/day. Due to intolerable side effects acetazolamide was replaced by topiramate, 125 mg/day in one patient. Treatment with acetazolamide and topiramate was paused respectively three and seven days before the 3-month follow-up examinations.

Infrequent (<14 days/month) use of simple analgesics (paracetamol and/or acetylsalicylic acid) was allowed. Treatment did not include use of opiate analgesics or tranquilizers.

Weight-loss was strongly recommended and patients were offered dietician consultations.

ICP

ICP was measured at baseline and at the 3-month follow-up. In one patient ICP was measured by direct intracranial pressure monitoring. In the remaining patients (n=30) ICP was measured by standardized lumbar puncture manometry. Patients were placed in lateral decubital position, had their legs straightened and were given a minimum of 10 min to relax before a stabilized pressure was recorded.

Cognitive testing

We assessed cognitive function by a neuropsychological test battery of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB))[9] and paper-and-pencil tests.

Paper-and-pencil tests: (a) **Rey – Osterreith's Complex Figure Test**, testing visuospatial memory; (b) **Trail Making Test A and B**, primarily testing psychomotor speed; (c) **Symbol Digit Modalities Test,** testing psychomotor speed; (d) **Verbal Fluency Test,** testing verbal semantic and phonological

fluency. The letters "S" and "A" and the categories "animals" and "items in a supermarket" were used.

CANTAB computerized tests: (e) **Motor screening test** to familiarize subjects with the touch screen; (f) **Spatial Span**, assessing visuospatial working memory span; (g) **Spatial Working Memory**, testing the ability to retain and manipulate spatial information in working memory; (h) **Stockings of Cambridge**, assessing spatial planning ability; (i) **Intra-Extra Dimensional Set Shift,** testing cognitive flexibility, requiring the formation and shifting of attentional set; (j) **Reaction Time**, assessing motor and reaction time latencies; (k) **Rapid Visual Information Processing**, testing sustained attention with a working memory load.

The **Danish Adult Reading Test** (Danish version of the National Adult Reading Test) was applied as an estimate of premorbid intelligence.[10]

The test battery was administered in a fixed order by the same physician (HY), instructed and trained by experienced neuro-psychologists (HF, BF). To ensure uniform test instructions we used a written instruction-manual during all sessions. Headache intensity at time of testing was recorded by a 10-point Visual Analogue Scale (VAS). Patients were re-tested at the 3-month follow-up.

Statistical analysis

Statistical analyses were conducted using SAS 9.3. Significance levels were set at 0.05. Non-normal distributed data were logarithmically transformed to reduce skewness. Categorical data were investigated by Chi-square test, Fishers' exact test and McNemar test.

Test-scores of patients and healthy controls were compared using a linear mixed model adjusting for education and headache at time of testing. Changes in patient test-scores from baseline to follow-up were analyzed in a linear mixed model for paired data adjusting for headache at time of testing. Test performance in patients with normalized ICP at follow-up and patient with continuous elevated ICP

was compared in a mixed model using ICP ≤25 cmH_2O and ICP<25 cmH_2O as a binary categorical variable. In addition the effect of ICP change (as a continuous variable) on difference in test performance from baseline to follow-up was analyzed.

The effects of depression and chronic pain on cognitive performance were explored within the patient group in a model comparing subjects with or without these traits, adjusting for education and headache at time of testing. The effect of BMI was explored in a similar model with BMI as a continuous variable.

To avoid effects of multiple comparisons in the analyses of cognitive function, the analyses were performed in mixed linear models including all 19 subtest scores into the same model.

For comparability of test-scores and evaluation of effect sizes, test-scores were standardized into z-scores. Z-scores were based on performance of the healthy controls which by definition had a mean scale score of zero and SD set to one. All scales were computed so that a higher z-score indicate better performance.

We used standardized test-scores to create composite domain scores, calculated by grouping selected tests, based on which cognitive domain they theoretically represented. Z-scores for cognitive domains were averaged and re-standardized based on the composite domain average and standard deviation of healthy controls.

Although they spoke Danish fluently, Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from statistical analysis as these test are potentially influenced by language-fluency and familiarity with the Latin alphabet. In domain construction the average of the remaining tests was used to determine the domain score.

RESULTS

Demographics and clinical characteristics at baseline

Patients and healthy controls did not differ in demographics, household income, educational level or premorbid intelligence level (Table 1). However, patient had significantly higher BMI and slightly less education counted in years than healthy controls.

Headache at the time of testing was reported by the majority of patients, but by none of the controls (Table 1). General headache disability in patients was heterogeneous. Ten patients fulfilled the criteria of chronic headache (≥15 days/month for 3 months)[7], four patients had frequent headache (mean 7.7 days/month)[7], seven had infrequent headache (<1 day /month)[7], 14 had only had headache in the weeks up until diagnosis and four patient had no headache at all. Healthy controls reported infrequent headaches with a mean frequency at 0.5 days/month.

Visual fields (Automated perimetry, Humprey 30-2) were bilaterally normal in 14 patients and normal in at least one eye in another eight patients. Seven patients had mild bilateral peripheral defects. One patient had bilateral concentric defects with remaining 15-20 central degrees of vision. In the cognitive tests this patient performed equally to the average patient. No photophobia or visual disturbances were reported during testing.

Depression (explicitly specified in the standardized interview) was reported by 8 (26%). Other co-morbidities included tension-type headache (n=12), migraine (n=7), diabetes (n=2), hypertension (n=2), inflammatory bowel disease (n=2), mild personality disorder (n=1), asthma (n=1), fibromyalgia (n=1), small pineal gland cyst (n=1)(asymptomatic, discovered on routine MR at time of IIH-diagnosis), sequela after monocular central serous choriorethinopathy (n=1), intermittent claudication (n=1), lumbar disc herniation (n=1).

Twenty-two patients were on either short term (n=18) or long-term sick-leave (n=4), five were unemployed and three had retired from work for reasons other than IIH.

Table 1. Demographics and clinical characteristics for IIH patients at baseline and at follow-up and healthy controls

	IIH Baseline n=31	IIH Follow-up n=29	Controls n=31	Statistics p[d]	p[e]
Demographics					
Age (SD), *years*	31.0 (11.2)		30.7 (11.2)	0.91	
Gender, *f*/m	31/0		31/0		
Danish Adult Reading Test (SD), *words*	22.9 (6.8)		24.8 (5.3)	0.15	
Education (SD), *years*	11.2 (2.2)		12.8 (2.1)	**0.001**	
Educational level				0.38	
Long cycle higher (≥ 5 years), *n*	0		3		
Medium cycle higher (3–5 years), *n*	4		7		
Short cycle higher (<3years), *n*	4		4		
Vocational upper- secondary, *n*	5		3		
Student, *n*	10		10		
No education, *n*	8		4		
Household income				0.81	
High (>DKK 400,000/year), *n*	10		8		
Middle (DKK 200-400,000/year), *n*	12		12		
Low (<DKK 200,000/year), *n*	9		11		
Clinical Characteristics					
BMI (SD), kg/m^2	35.7 (6.2)	34.0 (6.0)	23.6 (4.0)	**<0.001**	**0.009**
Headache at time of testing, *n (%)*	22 (71)	14 (48)	0		
Mean headache intensity (SD), *VAS*	2.64 (2.3)	1.84 (2.4)			**0.01**
ICP ↔ cognitive testing[a] (SD), *days*	3 (2.4)	1 (1.6)			
Mean ICP[b] (SD), cmH_2O	41.0 (12.6)	25.9 (5.5)			**<0.001**
Memory difficulties[c], *n (%)*	17 (55)	18 (62)			0.42

Concentration difficulties[c], *n (%)*	20 (65)	15 (52)	0.18
Duration of IIH symptoms (SD), *months*	4.34 (5.4)		

Chi-square test was used for household income, Fishers' exact test for educational level and McNemars'test for paired categorical variables. 2-tailed T-test was used for numerical variables. Significant p-values are printed in bold. [a]Time-span between ICP measurement and cognitive testing. [b]ICP measured with intracranial pressure monitor (n=1) not included. [c]Subjective difficulties reported by the patients. p[d]: difference between patients at baseline and healthy controls. p[e]: difference between patients at baseline and follow-up.

Cognitive function in patients at baseline

IIH-patients performed significantly worse than controls in four of six cognitive domains and in 13 of 19 subtests (Table 2). The most pronounced deficits were found in the domains of processing speed and reaction time (Figure 1). Even though deficits in executive functions only reached trend levels of significance patients scored significantly worse in the subtest measuring cognitive flexibility (ID/ED errors). Likewise, patients performed significantly worse in the subtest measuring spatial working memory strategy although no overall deficits in working memory was found. Sub-analyses within the patients group showed no difference between patients with or without depression or with or without chronic headache. Performance in cognitive tests within the patient group did was not related to BMI (ranging from 24.2 – 48.8 kg/m^2).

Table 2. Cognitive test scores and composite domain scores at baseline compared to healthy controls

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	Healthy Controls			
	n=31	n=31	Z	95% CL	p
Executive function			-0.61	-1.25;0.02	0.059
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors^{log}	8.1 (0-32)	4.0 (0-25)	-0.94	-1.54;-0.35	**0.002**
Total errors adjusted^{log},	20.9 (7-177)	12.2 (7-55)	-0.91	-1.50;-0.32	**0.003**
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	10.19 (1.7)	-0.28	-0.87;0.31	0.31
Initial thinking time^{log}, *s*	6.5 (2.0-18.3)	8.2 (3.1-40.7)	0.49	-0.11;1.08	0.11
Subsequent thinking time^{log}, *s*	0.013 (0-3.7)	0.011 (0-3.0)	0.09	-0.51;0.68	0.77
Trail Making Test[a]					
Trail Making B-A^{log}, *s*	39.2 (14.7-101.1)	30.62 (16.3-98.4)	-0.56	-1.10;0.09	0.07
Working memory			-0.56	-1.19;0.08	0.08
Spatial Working Memory					
Strategy score^{log}	29.9 (20-42)	24.8 (19-40)	-0.75	-1.35;-0.16	**0.01**
Total errors^{log}	10.2 (0-79)	4.7 (0-70)	-0.48	-1.07;0.12	0.11
Spatial Span:					
Span length	6.4 (1.3)	7.0 (1.4)	-0.31	-0.90;0.28	0.31
Processing speed			-1.45	-2.08;-0.81	**<0.0001**
Verbal Fluency[a]					
Letters	19.4 (7.0)	30.3 (8.3)	-1.25	-1.84;-0.65	**<0.0001**
Categories	39.8 (9.9)	55.5 (12.3)	-1.21	-1.81;-0.61	**<0.0001**

Trail Making Test[a]					
Trail Making A[log], *s*	31.5 (18.0-68.1)	25.2 (12.8-51.4)	-0.63	-1.22;-0.02	**0.04**
Trail Making B[log], *s*	73.5 (40.9-169.2)	52.2 (31.2-131.1)	-0.66	-1.26;-0.07	**0.02**
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	58.7 (9.0)	-1.09	-1.68;-0.49	**0.0003**
Visuospatial memory			-0.74	-1.32;-0.05	**0.02**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.0 (4.3)	-0.67	-1.26;-0.08	**0.03**
Delayed recall, *score*	23.8 (5.0)	28.0 (4.4)	-0.83	-1.42;-0.24	**0.006**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.93 (0.1)	-0.70	-1.30;-0.11	**0.01**
Reaction time			-1.48	-2.10;-0.85	**<0.0001**
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9-988.6)	330.0 (247.6-464.1)	-1.81	-2.40;-1.22	**<0.0001**
Movement, *ms*	417.8 (86.3)	338.3 (80.1)	-0.84	-1.43;-0.25	**0.006**

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis.

Clinical characteristics at follow-up

In spite of several invitations to attend a follow-up examination two patients dropped out from baseline to follow-up. Clinical characteristics and baseline test-scores in these 2 patients did not differ from the rest of the patient group.

Twenty-nine patients were reexamined at the 3-month follow-up. One patient refused to have lumbar puncture performed at follow-up. A normalized ICP was found in 14 of the remaining 28 patients. Less than half of the patients had headache during cognitive re-testing (Table 1). Visual fields were either stable or had improved from baseline.

Fourteen of 31 patients had resumed work/school, 11 patients were now on long-term sick-leave, one patient had reduced and altered work schedule due to IIH and two patients were unemployed.

Cognitive function at follow-up

After 3-months of treatment statistical significant improvement was detected in two domains (Table 3). Attention scores (RVP A') had practically normalized while performance in visouspatial memory tests improved to a level above performance in healthy controls.

No overall change was detected in the domains of executive function, working memory, processing speed and reaction time (Figure 2). Patients in which ICP had normalized (<25 cmH_2O) did not perform better than patients in which elevated ICP persisted (ICP>25 cmH_2O) and performance was not significantly associated with intensity or presence/absence of headache during the test. No correlation was found between change in cognitive performance and difference in ICP from baseline.

Table 3. Cognitive test scores and composite domain scores at follow-up compared to baseline

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline n=31	IIH Follow-up n=29	Z[b]	95% CL	p
Executive function			-0.18	-0.77;0.42	0.16
Intra-Extra Dimensional Set Shift					
ID/ED Errors[log]	8.1 (0–32)	5.8 (1–32)	-0.82	-1.40;-0.25	0.77
Total errors adjusted[log],	20.9 (7–177)	14.4 (7–68)	-0.56	-1.14;0.01	0.26
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	19.9 (2.0)	-0.08	-0.66;0.49	0.55
Initial thinking time[log], *s*	6.5 (2.0–18.3)	6.7 (2.5–18.4)	0.45	-0.14;1.02	0.98
Subsequent thinking time[log], *s*	0.013 (0–3.7)	0.013 (0–3.7)	0.11	-0.47;0.68	0.85
Trail Making Test[a]					
Trail Making B-A[log], *s*	39.2 (14.7–101.1)	33.1 (1.3–79.5)	0.46	-0.12;1.05	**0.002**
Working memory			-0.33	-0.84;0.18	0.44
Spatial Working Memory					
Strategy score[log]	29.9 (20-42)	27.9 (19–42)	-0.24	-0.81;0.34	0.10
Total errors[log]	10.2 (0–79)	10.1 (0–61)	-0.24	-0.81;0.34	0.50
Spatial Span:					
Span length	6.4 (1.3)	6.4 (1.3)	-0.27	-0.85;0.31	0.96
Processing speed			-1.23	-1.83;-0.64	0.49
Verbal Fluency[a]					
Letters	19.4 (7.0)	18.6 (6.6)	-1.27	-1.86;-0.69	0.88
Categories	39.8 (9.9)	42.5 (10.8)	-0.93	-1.51;-0.34	0.41

Trail Making Test[a]					
Trail Making A^{log}, *s*	31.5 (18.0–68.1)	32.9 (9.8)	-0.56	-1.15;0.02	0.95
Trail Making B^{log}, *s*	73.5 (40.9–169.2)	66.1 (38.7–125.4)	-0.18	-0.79;0.40	0.16
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	49.1 (12.3)	-0.91	-1.49;-0.33	0.50
Visuospatial memory			0.39	-0.17;1.02	**0.0005**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.9 (4.1)	0.36	-0.22;0.93	**0.002**
Delayed recall, *score*	23.8 (5.0)	28.8 (3.8)	0.31	-0.26;0.89	**0.0002**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.92 (0.04)	-0.14	-0.71;0.43	**0.03**
Reaction time			-1.31	-1.90;-0.71	0.90
Reaction Time:					
Reaction ^{log}, *ms*	409.4 (264.9–988.6)	387.4 (393.0–710.1)	-1.45	-2.02;-0.88	0.68
Movement, *ms*	417.8 (86.3)	412.3 (72.1)	-0.89	-1.46;-0.31	0.32

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables^{log} are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis. Z[b]: Patients at follow-up compared to healthy controls.

DISCUSSION

This study is the first to comprehensively explore the cognitive functions in a cohort of more than 10 patients with IIH. We examined 31 patients and found deficits in four of six cognitive domains suggesting that IIH is associated with a global cognitive dysfunction.

Cognitive function in IIH has only been reported in three studies[2-4] in addition to a single case-report[5]. One study[2] examined 85 patients but applied only a single memory test and the methodology was not described in details.. The remaining studies performed more extensive cognitive testing, but in contrast to our study were uncontrolled and included only respectively one, five and 10 patients[3-5] Prior studies were, in addition, based on patients with a wide range of disease duration (6-98 months) and only one study[3] reported ICP at time of testing. Our study is the first to assessed the cognitive function in a well-defined group of patients with newly diagnosed disease (n=29) or relapse (n=2).

While the case-study of Kaplan et al.[5] found no convincing cognitive deficits, Arseni et al.[2] and Kharkar et al.[4] reported substantial deficits in memory. We found deficits in visuospatial memory and in spatial working memory strategy, but detected no overall difference in working memory. Verbal memory (measured by Wecheler Memory Scale) was by far the most affected parameter in the study of Kharkar et al. and similarly was reported moderate to severe in 90% of the patients studied by Arseni et al. Although we did not test verbal memory we found significant deficits in other verbal functions (verbal fluency). This is in line with the study of Sorensen et al.[3] reporting verbal deficits in all of their five patients. Deficits in phonological fluency, which were substantial in our patients, have been shown to relate to frontal lobe damage, reflecting an additional executive component.[11]

The most severe deficits in our study were found in the domains of reaction time and processing speed which is consistent with the study of Sorensen et al.[3] In addition we found significant impairment in cognitive flexibility. Cognitive flexibility is fundamental for effective decision-making and the ability to learn and adapt to environmental changes, but has never been tested in patients with IIH before.

Although overall working memory was not affected in our study, patients did score significantly worse in the working memory strategy. This may reflect an executive component consistent with other executive deficits detected in our patients.

The deficits we detected in the domains of reaction time, processing speed, visuospatial memory and attention were equivalent to those found in patients with first episode schizophrenia.[12] In addition deficits in cognitive flexibility were similar to those (measured by Wisconsin Card Sort, a task conceptionally akin to the Intra-Extra Dimensional Set Shift Test) found in a meta-analyses of patients with schizophrenia in general.[13] Verbal fluency in our patients was affected to the same extents as reported for patients with schizophrenia[13] as well as patients with congentital hydrocephalus.[11] Furthermore deficits in verbal phonological fluency and processing speed (measured by Symbol Digit Modalities Test) were in the range found in patients with multiple sclerosis.[14-16]

Despite marked improvement in ICP and headache we found no convincing signs of overall cognitive improvement at the 3- month follow-up as the improvement seen in the visuospatial tests could be explained by test-retest effect (familiarization with the Rey Ostereith Complex Figure). Sorensen et al.[3] reported that although signs of cognitive dysfunction were only minor, four of their five patients were unable to manage work and/or everyday activities. In our study 12 of the 31 patients were either on long-term sick-leave or had reduced and altered work schedule due to IIH at follow up three months after diagnosis. Short follow-up and co-existent headache-symptoms limit

the interpretation of the socioeconomic impact of cognitive dysfunction demonstrated in our study. However, in other well recognized diseases such as schizophrenia a robust relationship between global and specific cognitive deficits and functional outcome has been consistently demonstrated.[17,18] The cause of cognitive impairment in IIH remains speculative. Theories could involve dysfunction of grey and/or white matter substance due to mechanical compression as proposed in normal pressure hydrocephalus,[11] dysfunction related to axonal flow as in optic nerve swelling and dysfunction[19] or release of cytotoxic substances as is seen in other conditions with cognitive decline.[20] Diffuse cerebral edema has been suggested by some[21,22] but refused by others.[23,24] High resolution imaging studies are still scarce, but as brain volume seems to be normal in IIH[25] we would expect any structural change that could explain the cognitive deficits found in this study to be subtle. Further high-resolution morphological imaging studies thus would be of great interest.

The strengths of the study is the prospective and controlled design, the broad range of cognitive tests, a relatively large study population, and the use of a culturally blind and computerized test battery that by automatic test conduction and score recording reduced the influence of the non-blinded observer. In addition the study population was well defined with cognitive testing performed in close relation to IIH diagnosis and ICP measurement. As patients were enrolled consecutively from both neurological and ophthalmological departments our study population reflects representative IIH-patients and not a selected group of cognitively symptomatic patients.

We recognize limitations to our study. First, the design was the non-blinded design and we did not perform retest of healthy controls. Secondly, the follow-up period was relatively short and may very well explain why we, unlike others,[3] failed to demonstrate improvement in cognitive function. Most importantly, although we adjusted for many of the most important confounders, our controls were not matched for BMI, headache or history of depression. The effect of headache on cognitive function has been debated,[26-28] but a recent comprehensive review concluded that there is no

evidence of cognitive dysfunction in patients with migraine in general.[29] On the other hand there seems to be evidence that *chronic* pain is associated with mild cognitive impairment in selected domains.[30,31] However, it is unclear if the cognitive impairment is attributed by the pain it self, or more likely mediated by co-existent depression.[32] Headache was chronic in 10 (32%) of our patients and depression was reported by eight (26%) patients. Neither depression nor chronic pain was associated with poorer cognitive performance when compared within the patient group. BMI in our patients ranged from normal to morbidly obese (24.2 – 48.8 kg/m^2). Patients with higher BMI did not perform worse than the less obese. It thus seems less likely that chronic pain, depression or obesity account for our findings of impaired cognition, but we fully acknowledge that ideally we should have included control group of obese patients with frequent headache in addition to the healthy subjects. The vide range of factors potentially affecting performance in cognitive tests, and the great variation within the patient group makes an ideal match very difficult to achieve. However, a feasible approach in obtaining phenotypically similar controls could be to recruit subjects with suspected IIH, but in which the diagnosis is declined after appropriate investigations.

In conclusions, this study strongly suggests that IIH is a disabling neurological disorder associated with cognitive deficits. The results in addition indicate that the cognitive deficits are long-lasting, not paralleling ICP and headache reduction, and are not sufficiently treated by diuretics and weight loss. Contrary to our hypothesis executive and memory functions were only moderately affected. Nevertheless we found substantial deficits in processing speed and reaction time which could explain some of the difficulties that patients encounter in work and daily activities. A focused multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with IIH.

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AUTHOR CONTRIBUTION

HMY made a substantive intellectual contribute to the design of the study, acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript.

BF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

HBF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

RHJ made a substantive intellectual contribute to the conceptualization and design of the study, the interpretation of the data and the revision of the manuscript.

COMPETING INTERESTS

H. Yri has received honoraria for consultant work from Neurocore and a travel grant from Berlin-Chemi Menarini. B. Fagerlund and H. Forchhammer report no disclosures. R. Jensen has received honoraria for lectures and patient leaflets from MSD, Berlin-Chemie Menarini, ATI and Pfizer and serves on medical advisory boards for LindeGas, ATI and Neurocore.

DATA SHARING STATEMENT

No additional data are available

EXCLUSIVE LICENCE

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FIGURE TITLES AND LEGENDS

Figur 1.

Title: Cognitive deficits in patients with IIH at time of diagnosis

Legends: Cognitive function in patients with IIH at time of diagnosis (n=31) shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. Colors indicate which domain the tests represent. *p<0.05 **p<0.005 ***p<0.0005.

Figure 2.

Title: Cognitive deficits in patients with IIH at time of diagnosis and at follow-up

Legends: Changes in test performance from time of diagnosis to follow-up (n=29) in patients with IIH shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. *p<0.05 **p<0.005 ***p<0.001.

Idiopathic intracranial hypertension is associated with cognitive dysfunction — a prospective case-control study

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ABSTRACT

Objective: To explore the extent and nature of cognitive deficits in patients with idiopathic intracranial hypertension at time of diagnosis and after three months of treatment.

Design: Prospective case-control study.

Setting: Neurological department, ophthalmological department and a tertiary headache referral clinic at a Danish university hospital**.**

Participants: Thirty-one patients with definite idiopathic intracranial hypertension referred from June 2011– February 2013 and included within one week of diagnostic intracranial pressure measurement. Twenty-nine patients completed re-examined at the 3-month follow-up. At time of testing none of the patients took medication potentially affecting cognitive function. Controls were 31 healthy age- and sex-matched volunteers from the local community.

Outcome measures: Executive function, working memory, visuospatial memory, processing speed, attention, and reaction time assessed by a comprehensive neuropsychological test battery consisting of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB)) and paper-and-pencil tests.

Results: Patients with idiopathic intracranial hypertension performed significantly worse than controls in four of six cognitive domains ($p \leq 0.02$). Deficits were most pronounced in reaction time (1.45 SD below controls 95% CI 2.10 to 0.85) and processing speed (1.45 SD below controls 95% CI 2.08 to 0.81). Despite marked improvement in intracranial pressure and headache, re-examination showed persistent cognitive dysfunction three months after diagnosis and start of treatment.

Conclusions: We demonstrate for the first time in a well-defined cohort of patients that idiopathic intracranial hypertension may be associated with cognitive dysfunction. This could explain the functional disability of patients with idiopathic intracranial hypertension. A focused

multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with idiopathic intracranial hypertension.

ARTICLE SUMMARY

Strengths and limitations of this study

- The first study to assess a broad range of cognitive functions in more than 10 patients
- Prospective controlled design and a well defined study population
- Controls were matched for age, sex and pre-morbid intelligence and in comparisons of cognitive measures we adjusted for education and headache at time of testing.
- The study was non-blinded and controls were not matched for Body Mass Index (BMI)
- Cognitive assessment by an automated computerized test battery reduced the influence of the non-blinded observer

INTRODUCTION

Due to predilection for young individuals of working age idiopathic intracranial hypertension (IIH) is a condition with substantial socioeconomic consequences. In USA alone the estimated annual costs exceed $444 million (> $17,000 /patient).[1] In addition to direct medical cost the major expenses was loss of wages caused by patients having to give up work or change profession due to IIH. Loss of income due to IIH is reported by 48% of patients,[1] but the exact cause of this substantial disability is yet unknown.

Despite obvious threat to visual function compliance with long-term treatment is often poor. In our clinics we experience a substantial lack of initiative and self-awareness in patients with IIH which has raised the suspicion of prefrontal dysfunction. However, while numerous studies describe the visual and headache-related complications of IIH, very little is known about the cognitive implications of the disease. Except for a single memory test conducted in 85 patients[2] the cognitive function in IIH has only been tested in a few very small study populations.[3-5] In all studies, apart from the case-report by Kaplan et al.,[5] testing revealed significant cognitive deficits in patients with IIH. Especially within verbal tests and memory deficits have been demonstrated.

The aim of this case-control study is to explore in details the extent and nature of cognitive deficits in patients with IIH at time of diagnosis and after three months of treatment.

METHODS

Subjects

We recruited 31 consecutive patients with IIH referred to the Department of Neuro-Ophthalmology, the Department of Neurology or the Danish Headache Center, Glostrup Hospital from June 2011–February 2013. Sample size was determined by the number of cases referred in the inclusion period. Twenty-eight of the patients were newly diagnosed with IIH, three patients had well-defined relapse

of IIH after a minimum of 10 months (range 10-26 months) of medication-free remission (resolved headache and papilledema). All patients had definite IIH according to the diagnostic criteria.[6,7] We included only patients that could be tested within seven days of confirmed diagnosis. Exclusion criteria were: other disorders or medication that could potentially affect cognition, decreased visual aquity, or language skills (Danish) deemed insufficient for participation in the cognitive assessment. Thirty-one healthy and headache free (defined as less than 4 headache days/month) controls, matched for age and sex, were recruited by advertising at Glostrup Hospital and on the website forsogspersonen.dk. Healthy controls were tested only once and did not have a lumbar puncture performed. Otherwise the cognitive examination program for patients and controls was identical.

Standard protocol approvals, registration and patients consents

All participants gave written, informed consent to participate in the study. The study was conducted in accordance with the declaration of Helsinki and approved by the Regional Ethics Committee.

General examination

At time of diagnosis patients underwent a complete neurological examination including MR/CT-imaging with venous sequences. All but one patient underwent thorough standardized neuro-ophthalmological examination.[8] The remaining patient did not participate in the neuro-opthalmological evaluation in spite of numerous invitations. A general ophthalmological examination was, however, performed at the local referring ophthalmological department.

Treatment

After diagnostic lumbar puncture and after cognitive testing was completed, treatment with acetazolamide was initiated. From baseline to 3-month follow-up doses were individually adjusted at doses of 750-2225 mg/day. Due to intolerable side effects acetazolamide was replaced by topiramate, 125 mg/day in one patient. Treatment with acetazolamide and topiramate was paused respectively three and seven days before the 3-month follow-up examinations.

Infrequent (<14 days/month) use of simple analgesics (paracetamol and/or acetylsalicylic acid) was allowed. Treatment did not include use of opiate analgesics or tranquilizers.

Weight-loss was strongly recommended and patients were offered dietician consultations.

ICP

ICP was measured at baseline and at the 3-month follow-up. In one patient ICP was measured by direct intracranial pressure monitoring. In the remaining patients (n=30) ICP was measured by standardized lumbar puncture manometry. Patients were placed in lateral decubital position, had their legs straightened and were given a minimum of 10 min to relax before a stabilized pressure was recorded.

Cognitive testing

We assessed cognitive function by a neuropsychological test battery of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB))[9] and paper-and-pencil tests.

Paper-and-pencil tests: (a) **Rey – Osterreith's Complex Figure Test**, testing visuospatial memory; (b) **Trail Making Test A and B**, primarily testing psychomotor speed; (c) **Symbol Digit Modalities Test,** testing psychomotor speed; (d) **Verbal Fluency Test,** testing verbal semantic and phonological

fluency. The letters "S" and "A" and the categories "animals" and "items in a supermarket" were used.

CANTAB computerized tests: (e) **Motor screening test** to familiarize subjects with the touch screen; (f) **Spatial Span**, assessing visuospatial working memory span; (g) **Spatial Working Memory**, testing the ability to retain and manipulate spatial information in working memory; (h) **Stockings of Cambridge**, assessing spatial planning ability; (i) **Intra-Extra Dimensional Set Shift,** testing cognitive flexibility, requiring the formation and shifting of attentional set; (j) **Reaction Time**, assessing motor and reaction time latencies; (k) **Rapid Visual Information Processing**, testing sustained attention with a working memory load.

The **Danish Adult Reading Test** (Danish version of the National Adult Reading Test) was applied as an estimate of premorbid intelligence.[10]

The test battery was administered in a fixed order by the same physician (HY), instructed and trained by experienced neuro-psychologists (HF, BF). To ensure uniform test instructions we used a written instruction-manual during all sessions. Headache intensity at time of testing was recorded by a 10-point Visual Analogue Scale (VAS). Patients were re-tested at the 3-month follow-up.

Statistical analysis

Statistical analyses were conducted using SAS 9.3. Significance levels were set at 0.05. Non-normal distributed data were logarithmically transformed to reduce skewness. Categorical data were investigated by Chi-square test, Fishers' exact test and McNemar test.

Test-scores of patients and healthy controls were compared using a linear mixed model adjusting for education and headache at time of testing. Changes in patient test-scores from baseline to follow-up were analyzed in a linear mixed model for paired data adjusting for headache at time of testing. Test performance in patients with normalized ICP at follow-up and patient with continuous elevated ICP

was compared in a mixed model using ICP ≤25 cmH_2O and ICP<25 cmH_2O as a binary categorical variable. In addition the effect of ICP change (as a continuous variable) on difference in test performance from baseline to follow-up was analyzed.

The effects of depression and chronic pain on cognitive performance were explored within the patient group in a model comparing subjects with or without these traits, adjusting for education and headache at time of testing. The effect of BMI was explored in a similar model with BMI as a continuous variable.

To avoid effects of multiple comparisons in the analyses of cognitive function, the analyses were performed in mixed linear models including all 19 subtest scores into the same model.

For comparability of test-scores and evaluation of effect sizes, test-scores were standardized into z-scores. Z-scores were based on performance of the healthy controls which by definition had a mean scale score of zero and SD set to one. All scales were computed so that a higher z-score indicate better performance.

We used standardized test-scores to create composite domain scores, calculated by grouping selected tests, based on which cognitive domain they theoretically represented. Z-scores for cognitive domains were averaged and re-standardized based on the composite domain average and standard deviation of healthy controls.

Although they spoke Danish fluently, Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from statistical analysis as these test are potentially influenced by language-fluency and familiarity with the Latin alphabet. In domain construction the average of the remaining tests was used to determine the domain score.

RESULTS

Demographics and clinical characteristics at baseline

Patients and healthy controls did not differ in demographics, household income, educational level or premorbid intelligence level (Table 1). However, patient had significantly higher BMI and slightly less education counted in years than healthy controls.

Headache at the time of testing was reported by the majority of patients, but by none of the controls (Table 1). General headache disability in patients was heterogeneous. Ten patients fulfilled the criteria of chronic headache (≥15 days/month for 3 months)[7], four patients had frequent headache (mean 7.7 days/month)[7], seven had infrequent headache (<1 day /month)[7], 14 had only had headache in the weeks up until diagnosis and four patient had no headache at all. Healthy controls reported infrequent headaches with a mean frequency at 0.5 days/month.

Visual fields (Automated perimetry, Humprey 30-2) were bilaterally normal in 14 patients and normal in at least one eye in another eight patients. Seven patients had mild bilateral peripheral defects. One patient had bilateral concentric defects with remaining 15-20 central degrees of vision. In the cognitive tests this patient performed equally to the average patient. No photophobia or visual disturbances were reported during testing.

Depression (explicitly specified in the standardized interview) was reported by 8 (26%). Other co-morbidities included tension-type headache (n=12), migraine (n=7), diabetes (n=2), hypertension (n=2), inflammatory bowel disease (n=2), mild personality disorder (n=1), asthma (n=1), fibromyalgia (n=1), small pineal gland cyst (n=1)(asymptomatic, discovered on routine MR at time of IIH-diagnosis), sequela after monocular central serous choriorethinopathy (n=1), intermittent claudication (n=1), lumbar disc herniation (n=1).

Twenty-two patients were on either short term (n=18) or long-term sick-leave (n=4), five were unemployed and three had retired from work for reasons other than IIH.

Table 1. Demographics and clinical characteristics for IIH patients at baseline and at follow-up and healthy controls

	IIH Baseline n=31	IIH Follow-up n=29	Controls n=31	Statistics p[d]	p[e]
Demographics					
Age (SD), *years*	31.0 (11.2)		30.7 (11.2)	0.91	
Gender, *f*/m	31/0		31/0		
Danish Adult Reading Test (SD), *words*	22.9 (6.8)		24.8 (5.3)	0.15	
Education (SD), *years*	11.2 (2.2)		12.8 (2.1)	**0.001**	
Educational level				0.38	
Long cycle higher (≥ 5 years), *n*	0		3		
Medium cycle higher (3–5 years), *n*	4		7		
Short cycle higher (<3years), *n*	4		4		
Vocational upper- secondary, *n*	5		3		
Student, *n*	10		10		
No education, *n*	8		4		
Household income				0.81	
High (>DKK 400,000/year), *n*	10		8		
Middle (DKK 200-400,000/year), *n*	12		12		
Low (<DKK 200,000/year), *n*	9		11		
Clinical Characteristics					
BMI (SD), kg/m^2	35.7 (6.2)	34.0 (6.0)	23.6 (4.0)	**<0.001**	**0.009**
Headache at time of testing, *n (%)*	22 (71)	14 (48)	0		
Mean headache intensity (SD), *VAS*	2.64 (2.3)	1.84 (2.4)			**0.01**
ICP ↔ cognitive testing[a] (SD), *days*	3 (2.4)	1 (1.6)			
Mean ICP[b] (SD), cmH_2O	41.0 (12.6)	25.9 (5.5)			**<0.001**
Memory difficulties[c], *n (%)*	17 (55)	18 (62)			0.42

Concentration difficulties[c], *n (%)*	20 (65)	15 (52)	0.18
Duration of IIH symptoms (SD), *months*	4.34 (5.4)		

Chi-square test was used for household income, Fishers' exact test for educational level and McNemars'test for paired categorical variables. 2-tailed T-test was used for numerical variables. Significant p-values are printed in bold. [a]Time-span between ICP measurement and cognitive testing. [b]ICP measured with intracranial pressure monitor (n=1) not included. [c]Subjective difficulties reported by the patients. p[d]: difference between patients at baseline and healthy controls. p[e]: difference between patients at baseline and follow-up.

Cognitive function in patients at baseline

IIH-patients performed significantly worse than controls in four of six cognitive domains and in 13 of 19 subtests (Table 2). The most pronounced deficits were found in the domains of processing speed and reaction time (Figure 1). Even though deficits in executive functions only reached trend levels of significance patients scored significantly worse in the subtest measuring cognitive flexibility (ID/ED errors). Likewise, patients performed significantly worse in the subtest measuring spatial working memory strategy although no overall deficits in working memory was found. Sub-analyses within the patients group showed no difference between patients with or without depression or with or without chronic headache. Performance in cognitive tests within the patient group did was not related to BMI (ranging from 24.2 – 48.8 kg/m^2).

Table 2. Cognitive test scores and composite domain scores at baseline compared to healthy controls

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline n=31	Healthy Controls n=31	Z	95% CL	p
Executive function			-0.61	-1.25;0.02	0.059
Intra-Extra Dimensional Set Shift					
ID/ED Errors^{log}	8.1 (0-32)	4.0 (0-25)	-0.94	-1.54;-0.35	**0.002**
Total errors adjusted^{log},	20.9 (7-177)	12.2 (7-55)	-0.91	-1.50;-0.32	**0.003**
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	10.19 (1.7)	-0.28	-0.87;0.31	0.31
Initial thinking time^{log}, *s*	6.5 (2.0-18.3)	8.2 (3.1-40.7)	0.49	-0.11;1.08	0.11
Subsequent thinking time^{log}, *s*	0.013 (0-3.7)	0.011 (0-3.0)	0.09	-0.51;0.68	0.77
Trail Making Test[a]					
Trail Making B-A^{log}, *s*	39.2 (14.7-101.1)	30.62 (16.3-98.4)	-0.56	-1.10;0.09	0.07
Working memory			-0.56	-1.19;0.08	0.08
Spatial Working Memory					
Strategy score^{log}	29.9 (20-42)	24.8 (19-40)	-0.75	-1.35;-0.16	**0.01**
Total errors^{log}	10.2 (0-79)	4.7 (0-70)	-0.48	-1.07;0.12	0.11
Spatial Span:					
Span length	6.4 (1.3)	7.0 (1.4)	-0.31	-0.90;0.28	0.31
Processing speed			-1.45	-2.08;-0.81	**<0.0001**
Verbal Fluency[a]					
Letters	19.4 (7.0)	30.3 (8.3)	-1.25	-1.84;-0.65	**<0.0001**
Categories	39.8 (9.9)	55.5 (12.3)	-1.21	-1.81;-0.61	**<0.0001**

Trail Making Test[a]					
Trail Making A[log], *s*	31.5 (18.0-68.1)	25.2 (12.8-51.4)	-0.63	-1.22;-0.02	**0.04**
Trail Making B[log], *s*	73.5 (40.9-169.2)	52.2 (31.2-131.1)	-0.66	-1.26;-0.07	**0.02**
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	58.7 (9.0)	-1.09	-1.68;-0.49	**0.0003**
Visuospatial memory			-0.74	-1.32;-0.05	**0.02**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.0 (4.3)	-0.67	-1.26;-0.08	**0.03**
Delayed recall, *score*	23.8 (5.0)	28.0 (4.4)	-0.83	-1.42;-0.24	**0.006**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.93 (0.1)	-0.70	-1.30;-0.11	**0.01**
Reaction time			-1.48	-2.10;-0.85	**<0.0001**
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9-988.6)	330.0 (247.6-464.1)	-1.81	-2.40;-1.22	**<0.0001**
Movement, *ms*	417.8 (86.3)	338.3 (80.1)	-0.84	-1.43;-0.25	**0.006**

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis.

Clinical characteristics at follow-up

In spite of several invitations to attend a follow-up examination two patients dropped out from baseline to follow-up. Clinical characteristics and baseline test-scores in these 2 patients did not differ from the rest of the patient group.

Twenty-nine patients were reexamined at the 3-month follow-up. One patient refused to have lumbar puncture performed at follow-up. A normalized ICP was found in 14 of the remaining 28 patients. Less than half of the patients had headache during cognitive re-testing (Table 1). Visual fields were either stable or had improved from baseline.

Fourteen of 31 patients had resumed work/school, 11 patients were now on long-term sick-leave, one patient had reduced and altered work schedule due to IIH and two patients were unemployed.

Cognitive function at follow-up

After 3-months of treatment statistical significant improvement was detected in two domains (Table 3). Attention scores (RVP A') had practically normalized while performance in visouspatial memory tests improved to a level above performance in healthy controls.

No overall change was detected in the domains of executive function, working memory, processing speed and reaction time (Figure 2). Patients in which ICP had normalized (<25 cmH_2O) did not perform better than patients in which elevated ICP persisted (ICP>25 cmH_2O) and performance was not significantly associated with intensity or presence/absence of headache during the test. No correlation was found between change in cognitive performance and difference in ICP from baseline.

Table 3. Cognitive test scores and composite domain scores at follow-up compared to baseline

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	IIH Follow-up			
	n=31	n=29	Z[b]	95% CL	p
Executive function			-0.18	-0.77;0.42	0.16
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors[log]	8.1 (0–32)	5.8 (1–32)	-0.82	-1.40;-0.25	0.77
Total errors adjusted[log],	20.9 (7–177)	14.4 (7–68)	-0.56	-1.14;0.01	0.26
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	19.9 (2.0)	-0.08	-0.66;0.49	0.55
Initial thinking time[log], *s*	6.5 (2.0–18.3)	6.7 (2.5–18.4)	0.45	-0.14;1.02	0.98
Subsequent thinking time[log], *s*	0.013 (0–3.7)	0.013 (0–3.7)	0.11	-0.47;0.68	0.85
Trail Making Test[a]					
Trail Making B-A[log], *s*	39.2 (14.7–101.1)	33.1 (1.3–79.5)	0.46	-0.12;1.05	**0.002**
Working memory			-0.33	-0.84;0.18	0.44
Spatial Working Memory					
Strategy score[log]	29.9 (20-42)	27.9 (19–42)	-0.24	-0.81;0.34	0.10
Total errors[log]	10.2 (0–79)	10.1 (0–61)	-0.24	-0.81;0.34	0.50
Spatial Span:					
Span length	6.4 (1.3)	6.4 (1.3)	-0.27	-0.85;0.31	0.96
Processing speed			-1.23	-1.83;-0.64	0.49
Verbal Fluency[a]					
Letters	19.4 (7.0)	18.6 (6.6)	-1.27	-1.86;-0.69	0.88
Categories	39.8 (9.9)	42.5 (10.8)	-0.93	-1.51;-0.34	0.41

Trail Making Test[a]					
Trail Making A^{log}, *s*	31.5 (18.0–68.1)	32.9 (9.8)	-0.56	-1.15;0.02	0.95
Trail Making B^{log}, *s*	73.5 (40.9–169.2)	66.1 (38.7–125.4)	-0.18	-0.79;0.40	0.16
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	49.1 (12.3)	-0.91	-1.49;-0.33	0.50
Visuospatial memory			0.39	-0.17;1.02	**0.0005**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.9 (4.1)	0.36	-0.22;0.93	**0.002**
Delayed recall, *score*	23.8 (5.0)	28.8 (3.8)	0.31	-0.26;0.89	**0.0002**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.92 (0.04)	-0.14	-0.71;0.43	**0.03**
Reaction time			-1.31	-1.90;-0.71	0.90
Reaction Time:					
Reaction ^{log}, *ms*	409.4 (264.9–988.6)	387.4 (393.0–710.1)	-1.45	-2.02;-0.88	0.68
Movement, *ms*	417.8 (86.3)	412.3 (72.1)	-0.89	-1.46;-0.31	0.32

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables^{log} are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis. Z[b]: Patients at follow-up compared to healthy controls.

DISCUSSION

This study is the first to comprehensively explore the cognitive functions in a cohort of more than 10 patients with IIH. We examined 31 patients and found deficits in four of six cognitive domains suggesting that IIH is associated with a global cognitive dysfunction.

Cognitive function in IIH has only been reported in three studies[2-4] in addition to a single case-report[5]. One study[2] examined 85 patients but applied only a single memory test and the methodology was not described in details.. The remaining studies performed more extensive cognitive testing, but in contrast to our study were uncontrolled and included only respectively one, five and 10 patients[3-5] Prior studies were, in addition, based on patients with a wide range of disease duration (6-98 months) and only one study[3] reported ICP at time of testing. Our study is the first to assessed the cognitive function in a well-defined group of patients with newly diagnosed disease (n=29) or relapse (n=2).

While the case-study of Kaplan et al.[5] found no convincing cognitive deficits, Arseni et al.[2] and Kharkar et al.[4] reported substantial deficits in memory. We found deficits in visuospatial memory and in spatial working memory strategy, but detected no overall difference in working memory. Verbal memory (measured by Wecheler Memory Scale) was by far the most affected parameter in the study of Kharkar et al. and similarly was reported moderate to severe in 90% of the patients studied by Arseni et al. Although we did not test verbal memory we found significant deficits in other verbal functions (verbal fluency). This is in line with the study of Sorensen et al.[3] reporting verbal deficits in all of their five patients. Deficits in phonological fluency, which were substantial in our patients, have been shown to relate to frontal lobe damage, reflecting an additional executive component.[11]

The most severe deficits in our study were found in the domains of reaction time and processing speed which is consistent with the study of Sorensen et al.[3] In addition we found significant impairment in cognitive flexibility. Cognitive flexibility is fundamental for effective decision-making and the ability to learn and adapt to environmental changes, but has never been tested in patients with IIH before.

Although overall working memory was not affected in our study, patients did score significantly worse in the working memory strategy. This may reflect an executive component consistent with other executive deficits detected in our patients.

The deficits we detected in the domains of reaction time, processing speed, visuospatial memory and attention were equivalent to those found in patients with first episode schizophrenia.[12] In addition deficits in cognitive flexibility were similar to those (measured by Wisconsin Card Sort, a task conceptionally akin to the Intra-Extra Dimensional Set Shift Test) found in a meta-analyses of patients with schizophrenia in general.[13] Verbal fluency in our patients was affected to the same extents as reported for patients with schizophrenia[13] as well as patients with congentital hydrocephalus.[11] Furthermore deficits in verbal phonological fluency and processing speed (measured by Symbol Digit Modalities Test) were in the range found in patients with multiple sclerosis.[14-16]

Despite marked improvement in ICP and headache we found no convincing signs of overall cognitive improvement at the 3- month follow-up as the improvement seen in the visuospatial tests could be explained by test-retest effect (familiarization with the Rey Ostereith Complex Figure). Sorensen et al.[3] reported that although signs of cognitive dysfunction were only minor, four of their five patients were unable to manage work and/or everyday activities. In our study 12 of the 31 patients were either on long-term sick-leave or had reduced and altered work schedule due to IIH at follow up three months after diagnosis. Short follow-up and co-existent headache-symptoms limit

the interpretation of the socioeconomic impact of cognitive dysfunction demonstrated in our study. However, in other well recognized diseases such as schizophrenia a robust relationship between global and specific cognitive deficits and functional outcome has been consistently demonstrated.[17,18] The cause of cognitive impairment in IIH remains speculative. Theories could involve dysfunction of grey and/or white matter substance due to mechanical compression as proposed in normal pressure hydrocephalus,[11] dysfunction related to axonal flow as in optic nerve swelling and dysfunction[19] or release of cytotoxic substances as is seen in other conditions with cognitive decline.[20] Diffuse cerebral edema has been suggested by some[21,22] but refused by others.[23,24] High resolution imaging studies are still scarce, but as brain volume seems to be normal in IIH[25] we would expect any structural change that could explain the cognitive deficits found in this study to be subtle. Further high-resolution morphological imaging studies thus would be of great interest.

The strengths of the study is the prospective and controlled design, the broad range of cognitive tests, a relatively large study population, and the use of a culturally blind and computerized test battery that by automatic test conduction and score recording reduced the influence of the non-blinded observer. In addition the study population was well defined with cognitive testing performed in close relation to IIH diagnosis and ICP measurement. As patients were enrolled consecutively from both neurological and ophthalmological departments our study population reflects representative IIH-patients and not a selected group of cognitively symptomatic patients.

We recognize limitations to our study. First, the design was the non-blinded design and we did not perform retest of healthy controls. Secondly, the follow-up period was relatively short and may very well explain why we, unlike others,[3] failed to demonstrate improvement in cognitive function. Most importantly, although we adjusted for many of the most important confounders, our controls were not matched for BMI, headache or history of depression. The effect of headache on cognitive function has been debated,[26-28] but a recent comprehensive review concluded that there is no

evidence of cognitive dysfunction in patients with migraine in general.[29] On the other hand there seems to be evidence that *chronic* pain is associated with mild cognitive impairment in selected domains.[30,31] However, it is unclear if the cognitive impairment is attributed by the pain it self, or more likely mediated by co-existent depression.[32] Headache was chronic in 10 (32%) of our patients and depression was reported by eight (26%) patients. Neither depression nor chronic pain was associated with poorer cognitive performance when compared within the patient group. BMI in our patients ranged from normal to morbidly obese (24.2 – 48.8 kg/m^2). Patients with higher BMI did not perform worse than the less obese. It thus seems less likely that chronic pain, depression or obesity account for our findings of impaired cognition, but we fully acknowledge that ideally we should have included control group of obese patients with frequent headache in addition to the healthy subjects. The vide range of factors potentially affecting performance in cognitive tests, and the great variation within the patient group makes an ideal match very difficult to achieve. However, a feasible approach in obtaining phenotypically similar controls could be to recruit subjects with suspected IIH, but in which the diagnosis is declined after appropriate investigations.

In conclusions, this study strongly suggests that IIH is a disabling neurological disorder associated with cognitive deficits. The results in addition indicate that the cognitive deficits are long-lasting, not paralleling ICP and headache reduction, and are not sufficiently treated by diuretics and weight loss. Contrary to our hypothesis executive and memory functions were only moderately affected. Nevertheless we found substantial deficits in processing speed and reaction time which could explain some of the difficulties that patients encounter in work and daily activities. A focused multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with IIH.

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COMPETING INTERESTS

H. Yri has received honoraria for consultant work from Neurocore and a travel grant from Berlin-Chemi Menarini. B. Fagerlund and H. Forchhammer report no disclosures. R. Jensen has received honoraria for lectures and patient leaflets from MSD, Berlin-Chemie Menarini, ATI and Pfizer and serves on medical advisory boards for LindeGas, ATI and Neurocore.

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AUTHOR CONTRIBUTION

HMY made a substantive intellectual contribute to the design of the study, acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript.

BF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

HBF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

RHJ made a substantive intellectual contribute to the conceptualization and design of the study, the interpretation of the data and the revision of the manuscript.

DATA SHARING STATEMENT

No additional data are available

EXCLUSIVE LICENCE

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FIGURE TITLES AND LEGENDS

Figur 1.

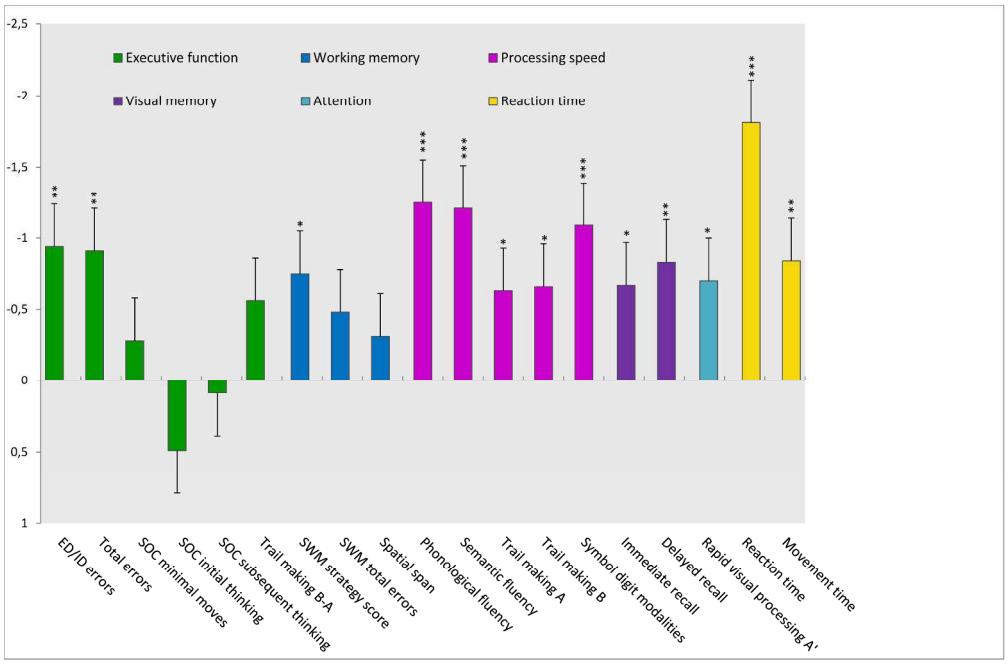
Title: Cognitive deficits in patients with IIH at time of diagnosis

Legends: Cognitive function in patients with IIH at time of diagnosis (n=31) shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. Colors indicate which domain the tests represent. *p<0.05 **p<0.005 ***p<0.0005.

Figure 2.

Title: Cognitive deficits in patients with IIH at time of diagnosis and at follow-up

Legends: Changes in test performance from time of diagnosis to follow-up (n=29) in patients with IIH shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. *p<0.05 **p<0.005 ***p<0.001.



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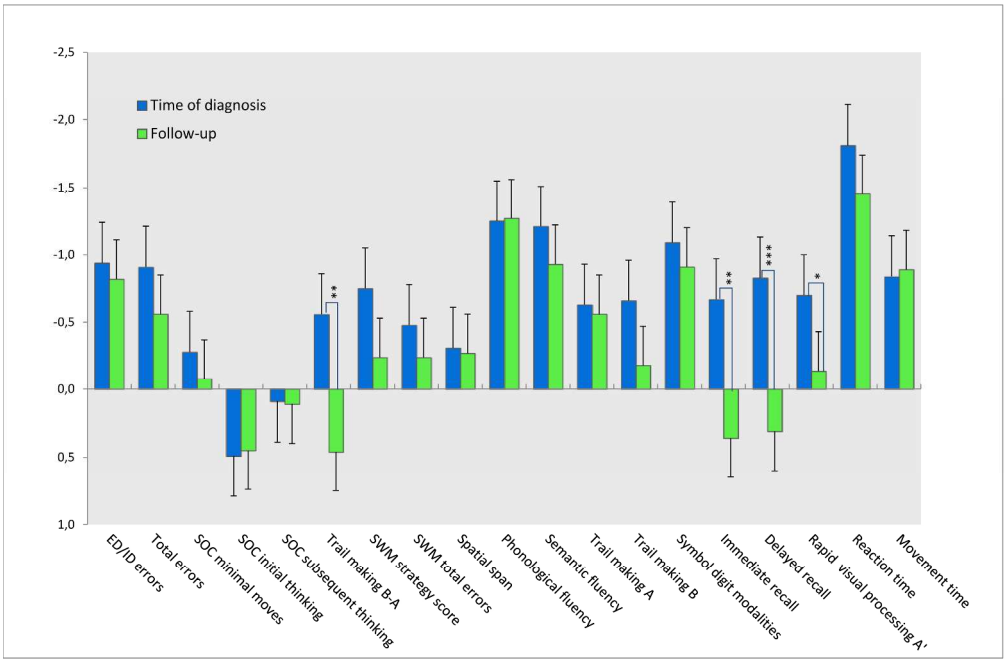

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls page 4-5
		(*b*) For matched studies, give matching criteria and the number of controls per case page 4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6-7
Bias	9	Describe any efforts to address potential sources of bias page 7-8
Study size	10	Explain how the study size was arrived at page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions page 7-8
		(*c*) Explain how missing data were addressed page 7-8
		(*d*) If applicable, explain how matching of cases and controls was addressed page 5
		(*e*) Describe any sensitivity analyses not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10,14,15
		(b) Give reasons for non-participation at each stage page14
		(c) Consider use of a flow diagram not applied
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10-11
		(b) Indicate number of participants with missing data for each variable of interest page 11,13,16
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure page 10,14,15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10-16
		(*b*) Report category boundaries when continuous variables were categorized page 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 14
Discussion		
Key results	18	Summarise key results with reference to study objectives page 17-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 20
Generalisability	21	Discuss the generalisability (external validity) of the study results page 18-20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 21

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Cognitive function in idiopathic intracranial hypertension — a prospective case-control study

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Cognitive function in idiopathic intracranial hypertension— a prospective case-control study

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KEY WORDS

Idiopathic intracranial hypertension, pseudotumor cerebri, cognition disorders, case-control studies.

WORD COUNT: 3210

NUMBER OF REFERENCES: 29

ABSTRACT

Objective: To explore the extent and nature of cognitive deficits in patients with idiopathic intracranial hypertension at time of diagnosis and after three months of treatment.

Design: Prospective case-control study.

Setting: Neurological department, ophthalmological department and a tertiary headache referral clinic at a Danish university hospital**.**

Participants: Thirty-one patients with definite idiopathic intracranial hypertension referred from June 2011– February 2013 and included within one week of diagnostic intracranial pressure measurement. Twenty-nine patients completed re-examination at the 3-month follow-up. At time of testing none of the patients took medication potentially affecting cognitive function. Controls were 31 healthy age- and sex-matched volunteers from the local community.

Outcome measures: Executive function, working memory, visuospatial memory, processing speed, attention, and reaction time assessed by a comprehensive neuropsychological test battery consisting of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB)) and paper-and-pencil tests.

Results: Patients with idiopathic intracranial hypertension performed significantly worse than controls in four of six cognitive domains ($p \leq 0.02$). Deficits were most pronounced in reaction time (1.45 SD below controls 95% CI 2.10 to 0.85) and processing speed (1.48 SD below controls 95% CI 2.08 to 0.81). Despite marked improvement in intracranial pressure and headache, re-examination showed persistent cognitive dysfunction three months after diagnosis and start of treatment.

Conclusions: We demonstrate for the first time in a well-defined cohort of patients that idiopathic intracranial hypertension may be associated with cognitive dysfunction. This could explain the functional disability of patients with idiopathic intracranial hypertension. A focused

multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with idiopathic intracranial hypertension.

ARTICLE SUMMARY

Strengths and limitations of this study

- The first study to assess a broad range of cognitive functions in more than 10 patients
- Prospective controlled design and a well defined study population
- Controls were matched for age, sex and pre-morbid intelligence and in comparisons of cognitive measures we adjusted for education and headache at time of testing.
- The study was non-blinded and controls were not matched for Body Mass Index (BMI)
- Cognitive assessment by an automated computerized test battery reduced the influence of the non-blinded observer

INTRODUCTION

Due to predilection for young individuals of working age idiopathic intracranial hypertension (IIH) is a condition with substantial socioeconomic consequences. In USA alone the estimated annual costs exceed $444 million (> $17,000 /patient).[1] In addition to direct medical cost the major expenses is loss of wages caused by patients having to give up work or change profession due to IIH. Loss of income due to IIH is reported by 48% of patients,[1] but the exact cause of this substantial disability is yet unknown.

Despite obvious threat to visual function compliance with long-term treatment is often poor. In our clinics we experience a substantial lack of initiative and self-awareness in patients with IIH which has raised the suspicion of prefrontal dysfunction. However, while numerous studies describe the visual and headache-related complications of IIH, very little is known about the cognitive implications of the disease. Except for a single memory test conducted in 85 patients[2] the cognitive function in IIH has only been tested in a few very small study populations.[3-5] In all studies, apart from the case-report by Kaplan et al.,[5] testing revealed significant cognitive deficits in patients with IIH. Especially within verbal tests and memory deficits have been demonstrated.

The aim of this case-control study is to explore in details the extent and nature of cognitive deficits in patients with IIH at time of diagnosis and after three months of treatment.

METHODS

Subjects

We recruited 31 consecutive patients with IIH referred to the Department of Neuro-Ophthalmology, the Department of Neurology or the Danish Headache Center, Glostrup Hospital from June 2011–February 2013. Sample size was determined by the number of cases referred in the inclusion period. Twenty-eight of the patients were newly diagnosed with IIH, three patients had well-defined relapse

of IIH after a minimum of 10 months (range 10-26 months) of medication-free remission (resolved headache and papilledema). All patients had definite IIH according to the diagnostic criteria.[6,7] We included only patients that could be tested within seven days of confirmed diagnosis. Exclusion criteria were: other disorders or medication that could potentially affect cognition, decreased visual aquity, or language skills (Danish) deemed insufficient for participation in the cognitive assessment. Thirty-one healthy and headache free (defined as less than 4 headache days/month) controls, matched for age and sex, were recruited by advertising at Glostrup Hospital and on the website forsogspersonen.dk. Healthy controls were tested only once and did not have a lumbar puncture performed. Otherwise the cognitive examination program for patients and controls was identical.

Standard protocol approvals, registration and patients consents

All participants gave written, informed consent to participate in the study. The study was conducted in accordance with the declaration of Helsinki and approved by the Regional Ethics Committee.

General examination

At time of diagnosis patients underwent a complete neurological examination including MR/CT-imaging with venous sequences. All but one patient underwent thorough standardized neuro-ophthalmological examination.[8] The remaining patient did not participate in the neuro-opthalmological evaluation in spite of numerous invitations. A general ophthalmological examination was, however, performed at the local referring ophthalmological department.

Treatment

After diagnostic lumbar puncture and after cognitive testing was completed, treatment with acetazolamide was initiated. From baseline to 3-month follow-up doses were individually adjusted at doses of 750-2225 mg/day. Due to intolerable side effects acetazolamide was replaced by topiramate, 125 mg/day in one patient. Treatment with acetazolamide and topiramate was paused respectively three and seven days before the 3-month follow-up examinations.

Infrequent (<14 days/month) use of simple analgesics (paracetamol and/or acetylsalicylic acid) was allowed. Treatment did not include use of opiate analgesics or tranquilizers.

Weight-loss was strongly recommended and patients were offered dietician consultations.

ICP

ICP was measured at baseline and at the 3-month follow-up. In one patient ICP was measured by direct intracranial pressure monitoring. In the remaining patients (n=30) ICP was measured by standardized lumbar puncture manometry. Patients were placed in lateral decubital position, had their legs straightened and were given a minimum of 10 min to relax before a stabilized pressure was recorded.

Cognitive testing

We assessed cognitive function by a neuropsychological test battery of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB))[9] and paper-and-pencil tests.

Paper-and-pencil tests: (a) **Rey – Osterreith's Complex Figure Test**, testing visuospatial memory; (b) **Trail Making Test A and B**, primarily testing psychomotor speed; (c) **Symbol Digit Modalities Test,** testing psychomotor speed; (d) **Verbal Fluency Test,** testing verbal semantic and phonological

fluency. The letters "S" and "A" and the categories "animals" and "items in a supermarket" were used.

CANTAB computerized tests: (e) **Motor screening test** to familiarize subjects with the touch screen; (f) **Spatial Span**, assessing visuospatial working memory span; (g) **Spatial Working Memory**, testing the ability to retain and manipulate spatial information in working memory; (h) **Stockings of Cambridge**, assessing spatial planning ability; (i) **Intra-Extra Dimensional Set Shift,** testing cognitive flexibility, requiring the formation and shifting of attentional set; (j) **Reaction Time**, assessing motor and reaction time latencies; (k) **Rapid Visual Information Processing**, testing sustained attention with a working memory load.

The **Danish Adult Reading Test** (Danish version of the National Adult Reading Test) was applied as an estimate of premorbid intelligence.[10]

The test battery was administered in a fixed order by the same physician (HY), instructed and trained by experienced neuro-psychologists (HF, BF). To ensure uniform test instructions we used a written instruction-manual during all sessions. Headache intensity at time of testing was recorded by a 10-point Visual Analogue Scale (VAS). Patients were re-tested at the 3-month follow-up.

Statistical analysis

Statistical analyses were conducted using SAS 9.3. Significance levels were set at 0.05. Non-normal distributed data were logarithmically transformed to reduce skewness. Categorical data were investigated by Chi-square test, Fishers' exact test and McNemar test.

Test-scores of patients and healthy controls were compared using a linear mixed model adjusting for education and headache at time of testing. Changes in patient test-scores from baseline to follow-up were analyzed in a linear mixed model for paired data adjusting for headache at time of testing. Test performance in patients with normalized ICP at follow-up and patient with continuous elevated ICP

was compared in a mixed model using ICP ≤25 cmH_2O and ICP<25 cmH_2O as a binary categorical variable. In addition the effect of ICP change (as a continuous variable) on difference in test performance from baseline to follow-up was analyzed.

The effects of depression and chronic pain on cognitive performance within the patient group were explored in a model comparing subjects with or without these traits, adjusting for education and headache at time of testing. The effect of BMI was explored in a similar model with BMI as a continuous variable.

To avoid effects of multiple comparisons in the analyses of cognitive function, the analyses were performed in mixed linear models including all 19 subtest scores into the same model.

For comparability of test-scores and evaluation of effect sizes, test-scores were standardized into z-scores. Z-scores were based on performance of the healthy controls which by definition had a mean scale score of zero and SD set to one. All scales were computed so that a higher z-score indicate better performance.

We used standardized test-scores to create composite domain scores, calculated by grouping selected tests, based on which cognitive domain they theoretically represented. Z-scores for cognitive domains were averaged and re-standardized based on the composite domain average and standard deviation of healthy controls.

Although they spoke Danish fluently, Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from statistical analysis as these test are potentially influenced by language-fluency and familiarity with the Latin alphabet. In domain construction the average of the remaining tests was used to determine the domain score.

RESULTS

Demographics and clinical characteristics at baseline

Patients and healthy controls did not differ in demographics, household income, educational level or premorbid intelligence level (Table 1). However, patient had significantly higher BMI and slightly less education counted in years than healthy controls.

Headache at the time of testing was reported by the majority of patients, but by none of the controls (Table 1). General headache disability in patients was heterogeneous. Eleven patients fulfilled the criteria of chronic headache (≥15 days/month for 3 months)[7], four patients had frequent headache (mean 4.5 days/months)[7], 13 patients only had headaches in the weeks up until diagnosis and three patients reported no headache at all. Healthy controls reported infrequent headaches with a mean frequency at 0.5 days/month.

Visual fields (Automated perimetry, Humprey 30-2) were bilaterally normal in 14 patients and normal in at least one eye in another nine patients. Seven patients had mild bilateral peripheral defects. One patient had bilateral concentric defects with remaining 15-20 central degrees of vision. In the cognitive tests this patient performed equally to the average patient. No photophobia or visual disturbances were reported during testing.

Depression (explicitly specified in the standardized interview) was reported by eight (26%). Other co-morbidities included tension-type headache (n=12), migraine (n=7), diabetes (n=2), hypertension (n=2), inflammatory bowel disease (n=2), mild personality disorder (n=1), asthma (n=1), fibromyalgia (n=1), small pineal gland cyst (n=1)(asymptomatic, discovered on routine MR at time of IIH-diagnosis), sequela after monocular central serous choriorethinopathy (n=1), intermittent claudication (n=1), lumbar disc herniation (n=1).

Twenty-two patients were on either short term (n=18) or long-term sick-leave (n=4), five were unemployed and three had retired from work for reasons other than IIH.

Table 1. Demographics and clinical characteristics for IIH patients at baseline and at follow-up and healthy controls

	IIH Baseline n=31	IIH Follow-up n=29	Controls n=31	Statistics p[d]	p[e]
Demographics					
Age (SD), *years*	31.0 (11.2)		30.7 (11.2)	0.91	
Gender, *f/m*	31/0		31/0		
Danish Adult Reading Test (SD), *words*	22.9 (6.8)		24.8 (5.3)	0.15	
Education (SD), *years*	11.2 (2.2)		12.8 (2.1)	**0.001**	
Educational level				0.38	
Long cycle higher (≥ 5 years), *n*	0		3		
Medium cycle higher (3–5 years), *n*	4		7		
Short cycle higher (<3years), *n*	4		4		
Vocational upper- secondary, *n*	5		3		
Student, *n*	10		10		
No education, *n*	8		4		
Household income				0.81	
High (>DKK 400,000/year), *n*	10		8		
Middle (DKK 200-400,000/year), *n*	12		12		
Low (<DKK 200,000/year), *n*	9		11		
Clinical Characteristics					
BMI (SD), kg/m^2	35.7 (6.2)	34.0 (6.0)	23.6 (4.0)	**<0.001**	**0.009**
Headache at time of testing, *n (%)*	22 (71)	14 (48)	0		
Mean headache intensity (SD), *VAS*	2.64 (2.3)	1.84 (2.4)			**0.01**
ICP ↔ cognitive testing[a] (SD), *days*	3 (2.4)	1 (1.6)			
Mean ICP[b] (SD), cmH_2O	41.0 (12.6)	25.9 (5.5)			**<0.001**
Memory difficulties[c], *n (%)*	17 (55)	18 (62)			0.42

Concentration difficulties[c], *n (%)*	20 (65)	15 (52)	0.18
Duration of IIH symptoms (SD), *months*	4.34 (5.4)		

Chi-square test was used for household income, Fishers' exact test for educational level and McNemars'test for paired categorical variables. 2-tailed T-test was used for numerical variables. Significant p-values are printed in bold. [a]Time-span between ICP measurement and cognitive testing. [b]ICP measured with intracranial pressure monitor (n=1) not included. [c]Subjective difficulties reported by the patients. p[d]: difference between patients at baseline and healthy controls. p[e]: difference between patients at baseline and follow-up.

Cognitive function in patients at baseline

IIH-patients performed significantly worse than controls in four of six cognitive domains and in 13 of 19 subtests (Table 2). The most pronounced deficits were found in the domains of processing speed and reaction time (Figure 1). Even though deficits in executive functions only reached trend levels of significance patients scored significantly worse in the subtest measuring cognitive flexibility (ID/ED errors). Likewise, patients performed significantly worse in the subtest measuring spatial working memory strategy although no overall deficits in working memory was found. Sub-analyses within the patients group showed no significant difference between patients with or without depression (mean overall test difference 0.05 SD 95% CI -0.42 to 0.53, p=0.83) or with or without chronic headache (mean overall test difference 0.34 SD 95% CI -0.18 to 0.83, p=0.19). Performance in cognitive tests within the patient group did was not related to BMI (ranging from 24.2 – 48.8 kg/m^2) (difference pr kg/m^2: 0.05 SD 95% CI -0.02 to 0.04, p=0.60). Differences for each of the 19 individual subtests variables are specified in Table 4 (data supplement, online only).

Table 2. Cognitive test scores and composite domain scores at baseline compared to healthy controls

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline n=31	Healthy Controls n=31	Z	95% CL	p
Executive function			-0.61	-1.25;0.02	0.059
Intra-Extra Dimensional Set Shift					
ID/ED Errors^{log}	8.1 (0-32)	4.0 (0-25)	-0.94	-1.54;-0.35	**0.002**
Total errors adjusted^{log},	20.9 (7-177)	12.2 (7-55)	-0.91	-1.50;-0.32	**0.003**
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	10.19 (1.7)	-0.28	-0.87;0.31	0.31
Initial thinking time^{log}, *s*	6.5 (2.0-18.3)	8.2 (3.1-40.7)	0.49	-0.11;1.08	0.11
Subsequent thinking time^{log}, *s*	0.013 (0-3.7)	0.011 (0-3.0)	0.09	-0.51;0.68	0.77
Trail Making Test[a]					
Trail Making B-A^{log}, *s*	39.2 (14.7-101.1)	30.62 (16.3-98.4)	-0.56	-1.10;0.09	0.07
Working memory			-0.56	-1.19;0.08	0.08
Spatial Working Memory					
Strategy score^{log}	29.9 (20-42)	24.8 (19-40)	-0.75	-1.35;-0.16	**0.01**
Total errors^{log}	10.2 (0-79)	4.7 (0-70)	-0.48	-1.07;0.12	0.11
Spatial Span:					
Span length	6.4 (1.3)	7.0 (1.4)	-0.31	-0.90;0.28	0.31
Processing speed			-1.45	-2.08;-0.81	**<0.0001**
Verbal Fluency[a]					
Letters	19.4 (7.0)	30.3 (8.3)	-1.25	-1.84;-0.65	**<0.0001**
Categories	39.8 (9.9)	55.5 (12.3)	-1.21	-1.81;-0.61	**<0.0001**

Trail Making Test[a]					
Trail Making A[log], *s*	31.5 (18.0-68.1)	25.2 (12.8-51.4)	-0.63	-1.22;-0.02	**0.04**
Trail Making B[log], *s*	73.5 (40.9-169.2)	52.2 (31.2-131.1)	-0.66	-1.26;-0.07	**0.02**
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	58.7 (9.0)	-1.09	-1.68;-0.49	**0.0003**
Visuospatial memory			-0.74	-1.32;-0.05	**0.02**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.0 (4.3)	-0.67	-1.26;-0.08	**0.03**
Delayed recall, *score*	23.8 (5.0)	28.0 (4.4)	-0.83	-1.42;-0.24	**0.006**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.93 (0.1)	-0.70	-1.30;-0.11	**0.01**
Reaction time			-1.48	-2.10;-0.85	**<0.0001**
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9-988.6)	330.0 (247.6-464.1)	-1.81	-2.40;-1.22	**<0.0001**
Movement, *ms*	417.8 (86.3)	338.3 (80.1)	-0.84	-1.43;-0.25	**0.006**

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis.

Clinical characteristics at follow-up

In spite of several invitations to attend a follow-up examination two patients dropped out from baseline to follow-up. Clinical characteristics and baseline test-scores in these two patients did not differ from the rest of the patient group.

Twenty-nine patients were reexamined at the 3-month follow-up. One patient refused to have lumbar puncture performed at follow-up. A normalized ICP was found in 14 of the remaining 28 patients. Less than half of the patients had headache during cognitive re-testing (Table 1). Visual fields were either stable or had improved from baseline.

Fourteen of 31 patients had resumed work/school, 11 patients were now on long-term sick-leave, one patient had reduced and altered work schedule due to IIH and two patients were unemployed.

Cognitive function at follow-up

After 3-months of treatment statistical significant improvement was detected in two domains (Table 3). Attention scores (RVP A') had practically normalized while performance in visouspatial memory tests improved to a level above performance in healthy controls.

No overall change was detected in the domains of executive function, working memory, processing speed and reaction time (Figure 2). Patients in which ICP had normalized (<25 cmH_2O) did not perform better than patients in which elevated ICP persisted (ICP>25 cmH_2O) and performance was not significantly associated with intensity or presence/absence of headache during the test. No correlation was found between change in cognitive performance and difference in ICP from baseline.

Table 3. Cognitive test scores and composite domain scores at follow-up compared to baseline

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	IIH Follow-up			
	n=31	n=29	Z[b]	95% CL	p
Executive function			-0.18	-0.77;0.42	0.16
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors[log]	8.1 (0–32)	5.8 (1–32)	-0.82	-1.40;-0.25	0.77
Total errors adjusted[log],	20.9 (7–177)	14.4 (7–68)	-0.56	-1.14;0.01	0.26
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	19.9 (2.0)	-0.08	-0.66;0.49	0.55
Initial thinking time[log], *s*	6.5 (2.0–18.3)	6.7 (2.5–18.4)	0.45	-0.14;1.02	0.98
Subsequent thinking time[log], *s*	0.013 (0–3.7)	0.013 (0–3.7)	0.11	-0.47;0.68	0.85
Trail Making Test[a]					
Trail Making B-A[log], *s*	39.2 (14.7–101.1)	33.1 (1.3–79.5)	0.46	-0.12;1.05	**0.002**
Working memory			-0.33	-0.84;0.18	0.44
Spatial Working Memory					
Strategy score[log]	29.9 (20-42)	27.9 (19–42)	-0.24	-0.81;0.34	0.10
Total errors[log]	10.2 (0–79)	10.1 (0–61)	-0.24	-0.81;0.34	0.50
Spatial Span:					
Span length	6.4 (1.3)	6.4 (1.3)	-0.27	-0.85;0.31	0.96
Processing speed			-1.23	-1.83;-0.64	0.49
Verbal Fluency[a]					
Letters	19.4 (7.0)	18.6 (6.6)	-1.27	-1.86;-0.69	0.88
Categories	39.8 (9.9)	42.5 (10.8)	-0.93	-1.51;-0.34	0.41
Trail Making Test[a]					

Trail Making A^{log}, *s*	31.5 (18.0–68.1)	32.9 (9.8)	-0.56	-1.15;0.02	0.95
Trail Making B^{log}, *s*	73.5 (40.9–169.2)	66.1 (38.7–125.4)	-0.18	-0.79;0.40	0.16
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	49.1 (12.3)	-0.91	-1.49;-0.33	0.50
Visuospatial memory			0.39	-0.17;1.02	**0.0005**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.9 (4.1)	0.36	-0.22;0.93	**0.002**
Delayed recall, *score*	23.8 (5.0)	28.8 (3.8)	0.31	-0.26;0.89	**0.0002**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.92 (0.04)	-0.14	-0.71;0.43	**0.03**
Reaction time			-1.31	-1.90;-0.71	0.90
Reaction Time:					
Reaction ^{log}, *ms*	409.4 (264.9–988.6)	387.4 (393.0–710.1)	-1.45	-2.02;-0.88	0.68
Movement, *ms*	417.8 (86.3)	412.3 (72.1)	-0.89	-1.46;-0.31	0.32

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables^{log} are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis. Z^{b}: Patients at follow-up compared to healthy controls.

DISCUSSION

This study is the first to comprehensively explore the cognitive functions in a cohort of more than 10 patients with IIH. We examined 31 patients and found deficits in four of six cognitive domains suggesting that IIH is associated with a global cognitive dysfunction.

Cognitive function in IIH has only been reported in three studies[2-4] in addition to a single case-report[5]. One study[2] examined 85 patients but applied only a single memory test and the methodology was not described in details. The remaining studies performed more extensive cognitive testing, but in contrast to our study were uncontrolled and included only respectively one, five and 10 patients[3-5] Prior studies were, in addition, based on patients with a wide range of disease duration (6-98 months) and only one study[3] reported ICP at time of testing. Our study is the first to assessed the cognitive function in a well-defined group of patients with newly diagnosed disease (n=29) or relapse (n=2).

While the case-study of Kaplan et al.[5] found no convincing cognitive deficits, Arseni et al.[2] and Kharkar et al.[4] reported substantial deficits in memory. We found deficits in visuospatial memory and in spatial working memory strategy, but detected no overall difference in working memory. Verbal memory (measured by Wecheler Memory Scale) was by far the most affected parameter in the study of Kharkar et al. and similarly was reported moderate to severe in 90% of the patients studied by Arseni et al. Although we did not test verbal memory we found significant deficits in other verbal functions (verbal fluency). This is in line with the study of Sorensen et al.[3] reporting verbal deficits in all of their five patients. Deficits in phonological fluency, which were substantial in our patients, have been shown to relate to frontal lobe damage, reflecting an additional executive component.[11]

The most severe deficits in our study were found in the domains of reaction time and processing speed which is consistent with the study of Sorensen et al.[3] In addition we found significant

impairment in cognitive flexibility. Cognitive flexibility is fundamental for effective decision-making and the ability to learn and adapt to environmental changes, but has never been tested in patients with IIH before.

Although overall working memory was not affected in our study, patients did score significantly worse in the working memory strategy. This may reflect an executive component consistent with other executive deficits detected in our patients.

The deficits we detected in the domains of reaction time, processing speed, visuospatial memory and attention were equivalent to those found in patients with first episode schizophrenia.[12] In addition deficits in cognitive flexibility were similar to those (measured by Wisconsin Card Sort, a task conceptionally akin to the Intra-Extra Dimensional Set Shift Test) found in a meta-analyses of patients with schizophrenia in general.[13] Verbal fluency in our patients was affected to the same extents as reported for patients with schizophrenia[13] as well as patients with congentital hydrocephalus.[11] Furthermore deficits in verbal phonological fluency and processing speed (measured by Symbol Digit Modalities Test) were in the range found in patients with multiple sclerosis.[14-16]

Despite marked improvement in ICP and headache we found no convincing signs of overall cognitive improvement at the 3- month follow-up as the improvement seen in the visuospatial tests could be explained by test-retest effect (familiarization with the Rey Ostereith Complex Figure). Sorensen et al.[3] reported that although signs of cognitive dysfunction were only minor, four of their five patients were unable to manage work and/or everyday activities. In our study 12 of the 31 patients were either on long-term sick-leave or had reduced and altered work schedule due to IIH at follow-up three months after diagnosis. Short follow-up and co-existent headache-symptoms limit the interpretation of the socioeconomic impact of cognitive dysfunction demonstrated in our study.

However, in other well recognized diseases such as schizophrenia a robust relationship between global and specific cognitive deficits and functional outcome has been consistently demonstrated.[17,18] The cause of cognitive impairment in IIH remains speculative. Theories could involve dysfunction of grey and/or white matter substance due to mechanical compression as proposed in normal pressure hydrocephalus,[11] dysfunction related to axonal flow as in optic nerve swelling and dysfunction[19] or release of cytotoxic substances as is seen in other conditions with cognitive decline.[20] To date there is no plausible evidence for brain damage in IIH[21] and as brain volume seems to be normal in IIH[22] we would expect any structural change that could explain the cognitive deficits found in this study to be subtle.

The strengths of the study is the prospective and controlled design, the broad range of cognitive tests, a relatively large study population, and the use of a culturally blind and computerized test battery that by automatic test conduction and score recording reduced the influence of the non-blinded observer. In addition the study population was well defined with cognitive testing performed in close relation to IIH diagnosis and ICP measurement. As patients were enrolled consecutively from both neurological and ophthalmological departments our study population reflects representative IIH-patients and not a selected group of cognitively symptomatic patients.

We recognize limitations to our study. First, the design was the non-blinded design and we did not perform retest of healthy controls. Secondly, the follow-up period was relatively short and may very well explain why we, unlike others,[3] failed to demonstrate improvement in cognitive function. Most importantly, although we adjusted for many of the most important confounders, our controls were not matched for BMI, headache or history of depression. The effect of headache on cognitive function has been debated,[23-25] but a recent comprehensive review concluded that there is no evidence of cognitive dysfunction in patients with migraine in general.[26] On the other hand there seems to be evidence that *chronic* pain is associated with mild cognitive impairment in selected

domains.[27,28] However, it is unclear if the cognitive impairment is attributed by the pain it self, or more likely mediated by co-existent depression.[29] Headache was chronic in 10 (32%) of our patients and depression was reported by eight (26%) patients. Neither depression nor chronic pain was associated with poorer cognitive performance when compared within the patient group. BMI in our patients ranged from normal to morbidly obese (24.2 – 48.8 kg/m^2). Patients with higher BMI did not perform worse than the less obese. Although it thus seems less likely that chronic pain, depression or obesity account for our findings of impaired cognition, sub-analyses were limited by small sample and statistical uncertainty. We acknowledge that to account for the influence of these potential confounders we ideally should have included an additional control group of obese patients with frequent headache. However, the vide range of factors potentially affecting performance in cognitive tests, and the great variation within the patient group, makes an ideal match very difficult to achieve. For future studies a feasible approach to this challenge could be to recruit subjects with suspected IIH, but in which the diagnosis is declined after appropriate investigations.

In conclusions, this study strongly suggests that IIH is associated with cognitive deficits. The results in addition indicate that the cognitive deficits are long-lasting, not paralleling ICP and headache reduction, and are not sufficiently treated by diuretics and weight loss. Contrary to our hypothesis executive and memory functions were only moderately affected. Nevertheless we found substantial deficits in processing speed and reaction time which could explain some of the difficulties that patients encounter in work and daily activities. A focused multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with IIH.

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AUTHOR CONTRIBUTION

HMY made a substantive intellectual contribute to the design of the study, acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript.

BF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

HBF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

RHJ made a substantive intellectual contribute to the conceptualization and design of the study, the interpretation of the data and the revision of the manuscript.

COMPETING INTERESTS

H. Yri has received honoraria for consultant work from Neurocore and a travel grant from Berlin-Chemi Menarini. B. Fagerlund and H. Forchhammer report no disclosures. R. Jensen has received honoraria for lectures and patient leaflets from MSD, Berlin-Chemie Menarini, ATI and Pfizer and serves on medical advisory boards for LindeGas, ATI and Neurocore.

DATA SHARING STATEMENT

There are no additional unpublished data from the study.

EXCLUSIVE LICENCE

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FIGURE TITLES AND LEGENDS

Figure 1.

Title: Cognitive deficits in patients with IIH at time of diagnosis

Legends: Cognitive function in patients with IIH at time of diagnosis (n=31) shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. Colors indicate which domain the tests represent. *p<0.05 **p<0.005 ***p<0.0005.

Figure 2.

Title: Cognitive deficits in patients with IIH at time of diagnosis and at follow-up

Legends: Changes in test performance from time of diagnosis to follow-up (n=29) in patients with IIH shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. *p<0.05 **p<0.005 ***p<0.001.

Cognitive function in idiopathic intracranial hypertension— a prospective case-control study

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KEY WORDS

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ABSTRACT

Objective: To explore the extent and nature of cognitive deficits in patients with idiopathic intracranial hypertension at time of diagnosis and after three months of treatment.

Design: Prospective case-control study.

Setting: Neurological department, ophthalmological department and a tertiary headache referral clinic at a Danish university hospital**.**

Participants: Thirty-one patients with definite idiopathic intracranial hypertension referred from June 2011– February 2013 and included within one week of diagnostic intracranial pressure measurement. Twenty-nine patients completed re-examination at the 3-month follow-up. At time of testing none of the patients took medication potentially affecting cognitive function. Controls were 31 healthy age- and sex-matched volunteers from the local community.

Outcome measures: Executive function, working memory, visuospatial memory, processing speed, attention, and reaction time assessed by a comprehensive neuropsychological test battery consisting of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB)) and paper-and-pencil tests.

Results: Patients with idiopathic intracranial hypertension performed significantly worse than controls in four of six cognitive domains ($p \leq 0.02$). Deficits were most pronounced in reaction time (1.45 SD below controls 95% CI 2.10 to 0.85) and processing speed (1.48 SD below controls 95% CI 2.08 to 0.81). Despite marked improvement in intracranial pressure and headache, re-examination showed persistent cognitive dysfunction three months after diagnosis and start of treatment.

Conclusions: We demonstrate for the first time in a well-defined cohort of patients that idiopathic intracranial hypertension may be associated with cognitive dysfunction. This could explain the functional disability of patients with idiopathic intracranial hypertension. A focused

multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with idiopathic intracranial hypertension.

ARTICLE SUMMARY

Strengths and limitations of this study

- The first study to assess a broad range of cognitive functions in more than 10 patients
- Prospective controlled design and a well defined study population
- Controls were matched for age, sex and pre-morbid intelligence and in comparisons of cognitive measures we adjusted for education and headache at time of testing.
- The study was non-blinded and controls were not matched for Body Mass Index (BMI)
- Cognitive assessment by an automated computerized test battery reduced the influence of the non-blinded observer

INTRODUCTION

Due to predilection for young individuals of working age idiopathic intracranial hypertension (IIH) is a condition with substantial socioeconomic consequences. In USA alone the estimated annual costs exceed $444 million (> $17,000 /patient).[1] In addition to direct medical cost the major expenses is loss of wages caused by patients having to give up work or change profession due to IIH. Loss of income due to IIH is reported by 48% of patients,[1] but the exact cause of this substantial disability is yet unknown.

Despite obvious threat to visual function compliance with long-term treatment is often poor. In our clinics we experience a substantial lack of initiative and self-awareness in patients with IIH which has raised the suspicion of prefrontal dysfunction. However, while numerous studies describe the visual and headache-related complications of IIH, very little is known about the cognitive implications of the disease. Except for a single memory test conducted in 85 patients[2] the cognitive function in IIH has only been tested in a few very small study populations.[3-5] In all studies, apart from the case-report by Kaplan et al.,[5] testing revealed significant cognitive deficits in patients with IIH. Especially within verbal tests and memory deficits have been demonstrated.

The aim of this case-control study is to explore in details the extent and nature of cognitive deficits in patients with IIH at time of diagnosis and after three months of treatment.

METHODS

Subjects

We recruited 31 consecutive patients with IIH referred to the Department of Neuro-Ophthalmology, the Department of Neurology or the Danish Headache Center, Glostrup Hospital from June 2011–February 2013. Sample size was determined by the number of cases referred in the inclusion period. Twenty-eight of the patients were newly diagnosed with IIH, three patients had well-defined relapse

of IIH after a minimum of 10 months (range 10-26 months) of medication-free remission (resolved headache and papilledema). All patients had definite IIH according to the diagnostic criteria.[6,7] We included only patients that could be tested within seven days of confirmed diagnosis. Exclusion criteria were: other disorders or medication that could potentially affect cognition, decreased visual aquity, or language skills (Danish) deemed insufficient for participation in the cognitive assessment. Thirty-one healthy and headache free (defined as less than 4 headache days/month) controls, matched for age and sex, were recruited by advertising at Glostrup Hospital and on the website forsogspersonen.dk. Healthy controls were tested only once and did not have a lumbar puncture performed. Otherwise the cognitive examination program for patients and controls was identical.

Standard protocol approvals, registration and patients consents

All participants gave written, informed consent to participate in the study. The study was conducted in accordance with the declaration of Helsinki and approved by the Regional Ethics Committee.

General examination

At time of diagnosis patients underwent a complete neurological examination including MR/CT-imaging with venous sequences. All but one patient underwent thorough standardized neuro-ophthalmological examination.[8] The remaining patient did not participate in the neuro-opthalmological evaluation in spite of numerous invitations. A general ophthalmological examination was, however, performed at the local referring ophthalmological department.

Treatment

After diagnostic lumbar puncture and after cognitive testing was completed, treatment with acetazolamide was initiated. From baseline to 3-month follow-up doses were individually adjusted at doses of 750-2225 mg/day. Due to intolerable side effects acetazolamide was replaced by topiramate, 125 mg/day in one patient. Treatment with acetazolamide and topiramate was paused respectively three and seven days before the 3-month follow-up examinations.

Infrequent (<14 days/month) use of simple analgesics (paracetamol and/or acetylsalicylic acid) was allowed. Treatment did not include use of opiate analgesics or tranquilizers.

Weight-loss was strongly recommended and patients were offered dietician consultations.

ICP

ICP was measured at baseline and at the 3-month follow-up. In one patient ICP was measured by direct intracranial pressure monitoring. In the remaining patients (n=30) ICP was measured by standardized lumbar puncture manometry. Patients were placed in lateral decubital position, had their legs straightened and were given a minimum of 10 min to relax before a stabilized pressure was recorded.

Cognitive testing

We assessed cognitive function by a neuropsychological test battery of validated computerized (Cambridge Neuropsychological Test Automated Battery (CANTAB))[9] and paper-and-pencil tests.

Paper-and-pencil tests: (a) **Rey – Osterreith's Complex Figure Test**, testing visuospatial memory; (b) **Trail Making Test A and B**, primarily testing psychomotor speed; (c) **Symbol Digit Modalities Test,** testing psychomotor speed; (d) **Verbal Fluency Test,** testing verbal semantic and phonological

fluency. The letters "S" and "A" and the categories "animals" and "items in a supermarket" were used.

CANTAB computerized tests: (e) **Motor screening test** to familiarize subjects with the touch screen; (f) **Spatial Span**, assessing visuospatial working memory span; (g) **Spatial Working Memory**, testing the ability to retain and manipulate spatial information in working memory; (h) **Stockings of Cambridge**, assessing spatial planning ability; (i) **Intra-Extra Dimensional Set Shift,** testing cognitive flexibility, requiring the formation and shifting of attentional set; (j) **Reaction Time**, assessing motor and reaction time latencies; (k) **Rapid Visual Information Processing**, testing sustained attention with a working memory load.

The **Danish Adult Reading Test** (Danish version of the National Adult Reading Test) was applied as an estimate of premorbid intelligence.[10]

The test battery was administered in a fixed order by the same physician (HY), instructed and trained by experienced neuro-psychologists (HF, BF). To ensure uniform test instructions we used a written instruction-manual during all sessions. Headache intensity at time of testing was recorded by a 10-point Visual Analogue Scale (VAS). Patients were re-tested at the 3-month follow-up.

Statistical analysis

Statistical analyses were conducted using SAS 9.3. Significance levels were set at 0.05. Non-normal distributed data were logarithmically transformed to reduce skewness. Categorical data were investigated by Chi-square test, Fishers' exact test and McNemar test.

Test-scores of patients and healthy controls were compared using a linear mixed model adjusting for education and headache at time of testing. Changes in patient test-scores from baseline to follow-up were analyzed in a linear mixed model for paired data adjusting for headache at time of testing. Test performance in patients with normalized ICP at follow-up and patient with continuous elevated ICP

was compared in a mixed model using ICP ≤25 cmH_2O and ICP<25 cmH_2O as a binary categorical variable. In addition the effect of ICP change (as a continuous variable) on difference in test performance from baseline to follow-up was analyzed.

The effects of depression and chronic pain on cognitive performance within the patient group were explored in a model comparing subjects with or without these traits, adjusting for education and headache at time of testing. The effect of BMI was explored in a similar model with BMI as a continuous variable.

To avoid effects of multiple comparisons in the analyses of cognitive function, the analyses were performed in mixed linear models including all 19 subtest scores into the same model.

For comparability of test-scores and evaluation of effect sizes, test-scores were standardized into z-scores. Z-scores were based on performance of the healthy controls which by definition had a mean scale score of zero and SD set to one. All scales were computed so that a higher z-score indicate better performance.

We used standardized test-scores to create composite domain scores, calculated by grouping selected tests, based on which cognitive domain they theoretically represented. Z-scores for cognitive domains were averaged and re-standardized based on the composite domain average and standard deviation of healthy controls.

Although they spoke Danish fluently, Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from statistical analysis as these test are potentially influenced by language-fluency and familiarity with the Latin alphabet. In domain construction the average of the remaining tests was used to determine the domain score.

RESULTS

Demographics and clinical characteristics at baseline

Patients and healthy controls did not differ in demographics, household income, educational level or premorbid intelligence level (Table 1). However, patient had significantly higher BMI and slightly less education counted in years than healthy controls.

Headache at the time of testing was reported by the majority of patients, but by none of the controls (Table 1). General headache disability in patients was heterogeneous. Eleven patients fulfilled the criteria of chronic headache (≥15 days/month for 3 months)[7], four patients had frequent headache (mean 4.5 days/months)[7], 13 patients only had headaches in the weeks up until diagnosis and three patients reported no headache at all. Healthy controls reported infrequent headaches with a mean frequency at 0.5 days/month.

Visual fields (Automated perimetry, Humprey 30-2) were bilaterally normal in 14 patients and normal in at least one eye in another nine patients. Seven patients had mild bilateral peripheral defects. One patient had bilateral concentric defects with remaining 15-20 central degrees of vision. In the cognitive tests this patient performed equally to the average patient. No photophobia or visual disturbances were reported during testing.

Depression (explicitly specified in the standardized interview) was reported by eight (26%). Other co-morbidities included tension-type headache (n=12), migraine (n=7), diabetes (n=2), hypertension (n=2), inflammatory bowel disease (n=2), mild personality disorder (n=1), asthma (n=1), fibromyalgia (n=1), small pineal gland cyst (n=1)(asymptomatic, discovered on routine MR at time of IIH-diagnosis), sequela after monocular central serous choriorethinopathy (n=1), intermittent claudication (n=1), lumbar disc herniation (n=1).

Twenty-two patients were on either short term (n=18) or long-term sick-leave (n=4), five were unemployed and three had retired from work for reasons other than IIH.

Table 1. Demographics and clinical characteristics for IIH patients at baseline and at follow-up and healthy controls

	IIH Baseline n=31	IIH Follow-up n=29	Controls n=31	Statistics p[d]	p[e]
Demographics					
Age (SD), *years*	31.0 (11.2)		30.7 (11.2)	0.91	
Gender, *f/m*	31/0		31/0		
Danish Adult Reading Test (SD), *words*	22.9 (6.8)		24.8 (5.3)	0.15	
Education (SD), *years*	11.2 (2.2)		12.8 (2.1)	**0.001**	
Educational level				0.38	
Long cycle higher (≥ 5 years), *n*	0		3		
Medium cycle higher (3–5 years), *n*	4		7		
Short cycle higher (<3years), *n*	4		4		
Vocational upper- secondary, *n*	5		3		
Student, *n*	10		10		
No education, *n*	8		4		
Household income				0.81	
High (>DKK 400,000/year), *n*	10		8		
Middle (DKK 200-400,000/year), *n*	12		12		
Low (<DKK 200,000/year), *n*	9		11		
Clinical Characteristics					
BMI (SD), kg/m^2	35.7 (6.2)	34.0 (6.0)	23.6 (4.0)	**<0.001**	**0.009**
Headache at time of testing, *n (%)*	22 (71)	14 (48)	0		
Mean headache intensity (SD), *VAS*	2.64 (2.3)	1.84 (2.4)			**0.01**
ICP ↔ cognitive testing[a] (SD), *days*	3 (2.4)	1 (1.6)			
Mean ICP[b] (SD), cmH_2O	41.0 (12.6)	25.9 (5.5)			**<0.001**
Memory difficulties[c], *n (%)*	17 (55)	18 (62)			0.42

Concentration difficulties[c], *n (%)*	20 (65)	15 (52)	0.18
Duration of IIH symptoms (SD), *months*	4.34 (5.4)		

Chi-square test was used for household income, Fishers' exact test for educational level and McNemars'test for paired categorical variables. 2-tailed T-test was used for numerical variables. Significant p-values are printed in bold. [a]Time-span between ICP measurement and cognitive testing. [b]ICP measured with intracranial pressure monitor (n=1) not included. [c]Subjective difficulties reported by the patients. p[d]: difference between patients at baseline and healthy controls. p[e]: difference between patients at baseline and follow-up.

Cognitive function in patients at baseline

IIH-patients performed significantly worse than controls in four of six cognitive domains and in 13 of 19 subtests (Table 2). The most pronounced deficits were found in the domains of processing speed and reaction time (Figure 1). Even though deficits in executive functions only reached trend levels of significance patients scored significantly worse in the subtest measuring cognitive flexibility (ID/ED errors). Likewise, patients performed significantly worse in the subtest measuring spatial working memory strategy although no overall deficits in working memory was found. Sub-analyses within the patients group showed no significant difference between patients with or without depression (mean overall test difference 0.05 SD 95% CI -0.42 to 0.53, p=0.83) or with or without chronic headache (mean overall test difference 0.34 SD 95% CI -0.18 to 0.83, p=0.19). Performance in cognitive tests within the patient group did was not related to BMI (ranging from 24.2 – 48.8 kg/m^2) (difference pr kg/m^2: 0.05 SD 95% CI -0.02 to 0.04, p=0.60). Differences for each of the 19 individual subtests variables are specified in Table 4 (data supplement, online only).

Table 2. Cognitive test scores and composite domain scores at baseline compared to healthy controls

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	Healthy Controls			
	n=31	n=31	Z	95% CL	p
Executive function			-0.61	-1.25;0.02	0.059
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors^{log}	8.1 (0-32)	4.0 (0-25)	-0.94	-1.54;-0.35	**0.002**
Total errors adjusted^{log},	20.9 (7-177)	12.2 (7-55)	-0.91	-1.50;-0.32	**0.003**
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	10.19 (1.7)	-0.28	-0.87;0.31	0.31
Initial thinking time^{log}, *s*	6.5 (2.0-18.3)	8.2 (3.1-40.7)	0.49	-0.11;1.08	0.11
Subsequent thinking time^{log}, *s*	0.013 (0-3.7)	0.011 (0-3.0)	0.09	-0.51;0.68	0.77
Trail Making Test[a]					
Trail Making B-A^{log}, *s*	39.2 (14.7-101.1)	30.62 (16.3-98.4)	-0.56	-1.10;0.09	0.07
Working memory			-0.56	-1.19;0.08	0.08
Spatial Working Memory					
Strategy score^{log}	29.9 (20-42)	24.8 (19-40)	-0.75	-1.35;-0.16	**0.01**
Total errors^{log}	10.2 (0-79)	4.7 (0-70)	-0.48	-1.07;0.12	0.11
Spatial Span:					
Span length	6.4 (1.3)	7.0 (1.4)	-0.31	-0.90;0.28	0.31
Processing speed			-1.45	-2.08;-0.81	**<0.0001**
Verbal Fluency[a]					
Letters	19.4 (7.0)	30.3 (8.3)	-1.25	-1.84;-0.65	**<0.0001**
Categories	39.8 (9.9)	55.5 (12.3)	-1.21	-1.81;-0.61	**<0.0001**

Trail Making Test[a]					
Trail Making A[log], *s*	31.5 (18.0-68.1)	25.2 (12.8-51.4)	-0.63	-1.22;-0.02	**0.04**
Trail Making B[log], *s*	73.5 (40.9-169.2)	52.2 (31.2-131.1)	-0.66	-1.26;-0.07	**0.02**
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	58.7 (9.0)	-1.09	-1.68;-0.49	**0.0003**
Visuospatial memory			-0.74	-1.32;-0.05	**0.02**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.0 (4.3)	-0.67	-1.26;-0.08	**0.03**
Delayed recall, *score*	23.8 (5.0)	28.0 (4.4)	-0.83	-1.42;-0.24	**0.006**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.93 (0.1)	-0.70	-1.30;-0.11	**0.01**
Reaction time			-1.48	-2.10;-0.85	**<0.0001**
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9-988.6)	330.0 (247.6-464.1)	-1.81	-2.40;-1.22	**<0.0001**
Movement, *ms*	417.8 (86.3)	338.3 (80.1)	-0.84	-1.43;-0.25	**0.006**

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis.

Clinical characteristics at follow-up

In spite of several invitations to attend a follow-up examination two patients dropped out from baseline to follow-up. Clinical characteristics and baseline test-scores in these two patients did not differ from the rest of the patient group.

Twenty-nine patients were reexamined at the 3-month follow-up. One patient refused to have lumbar puncture performed at follow-up. A normalized ICP was found in 14 of the remaining 28 patients. Less than half of the patients had headache during cognitive re-testing (Table 1). Visual fields were either stable or had improved from baseline.

Fourteen of 31 patients had resumed work/school, 11 patients were now on long-term sick-leave, one patient had reduced and altered work schedule due to IIH and two patients were unemployed.

Cognitive function at follow-up

After 3-months of treatment statistical significant improvement was detected in two domains (Table 3). Attention scores (RVP A') had practically normalized while performance in visouspatial memory tests improved to a level above performance in healthy controls.

No overall change was detected in the domains of executive function, working memory, processing speed and reaction time (Figure 2). Patients in which ICP had normalized (<25 cmH_2O) did not perform better than patients in which elevated ICP persisted (ICP>25 cmH_2O) and performance was not significantly associated with intensity or presence/absence of headache during the test. No correlation was found between change in cognitive performance and difference in ICP from baseline.

Table 3. Cognitive test scores and composite domain scores at follow-up compared to baseline

Test Variables	Raw-scores		Z-scores and statistics		
	IIH Baseline	IIH Follow-up			
	n=31	n=29	Z[b]	95% CL	p
Executive function			-0.18	-0.77;0.42	0.16
Intra-Extra Dimensional					
Set Shift					
ID/ED Errors[log]	8.1 (0–32)	5.8 (1–32)	-0.82	-1.40;-0.25	0.77
Total errors adjusted[log],	20.9 (7–177)	14.4 (7–68)	-0.56	-1.14;0.01	0.26
Stockings of Cambridge					
Solved in minimum moves	9.61 (2.0)	19.9 (2.0)	-0.08	-0.66;0.49	0.55
Initial thinking time[log], *s*	6.5 (2.0–18.3)	6.7 (2.5–18.4)	0.45	-0.14;1.02	0.98
Subsequent thinking time[log], *s*	0.013 (0–3.7)	0.013 (0–3.7)	0.11	-0.47;0.68	0.85
Trail Making Test[a]					
Trail Making B-A[log], *s*	39.2 (14.7–101.1)	33.1 (1.3–79.5)	0.46	-0.12;1.05	**0.002**
Working memory			-0.33	-0.84;0.18	0.44
Spatial Working Memory					
Strategy score[log]	29.9 (20-42)	27.9 (19–42)	-0.24	-0.81;0.34	0.10
Total errors[log]	10.2 (0–79)	10.1 (0–61)	-0.24	-0.81;0.34	0.50
Spatial Span:					
Span length	6.4 (1.3)	6.4 (1.3)	-0.27	-0.85;0.31	0.96
Processing speed			-1.23	-1.83;-0.64	0.49
Verbal Fluency[a]					
Letters	19.4 (7.0)	18.6 (6.6)	-1.27	-1.86;-0.69	0.88
Categories	39.8 (9.9)	42.5 (10.8)	-0.93	-1.51;-0.34	0.41
Trail Making Test[a]					

Trail Making A[log], *s*	31.5 (18.0–68.1)	32.9 (9.8)	-0.56	-1.15;0.02	0.95
Trail Making B[log], *s*	73.5 (40.9–169.2)	66.1 (38.7–125.4)	-0.18	-0.79;0.40	0.16
Symbol Digit Modalities					
Correct symbols	47.8 (10.2)	49.1 (12.3)	-0.91	-1.49;-0.33	0.50
Visuospatial memory			0.39	-0.17;1.02	**0.0005**
Rey-Osterreith Figure					
Immediate recall, *score*	24.5 (5.4)	28.9 (4.1)	0.36	-0.22;0.93	**0.002**
Delayed recall, *score*	23.8 (5.0)	28.8 (3.8)	0.31	-0.26;0.89	**0.0002**
Attention					
Rapid Visual Processing					
A' sensitivity to target	0.9 (0.1)	0.92 (0.04)	-0.14	-0.71;0.43	**0.03**
Reaction time			-1.31	-1.90;-0.71	0.90
Reaction Time:					
Reaction [log], *ms*	409.4 (264.9–988.6)	387.4 (393.0–710.1)	-1.45	-2.02;-0.88	0.68
Movement, *ms*	417.8 (86.3)	412.3 (72.1)	-0.89	-1.46;-0.31	0.32

Normally distributed raw-score variables are shown as mean (SD). Logarithmically transformed variables[log] are shown as arithmetic mean (range). Z-scores and test statistics are given in estimates from a linear mixed model adjusting for education and headache at time of testing and multiple testing. Significant p-values are printed in bold. [a]n=29, as Trail Making Test scores and Verbal Fluency scores from non-native Danish speakers (n=2) were omitted from analysis. Z[b]: Patients at follow-up compared to healthy controls.

DISCUSSION

This study is the first to comprehensively explore the cognitive functions in a cohort of more than 10 patients with IIH. We examined 31 patients and found deficits in four of six cognitive domains suggesting that IIH is associated with a global cognitive dysfunction.

Cognitive function in IIH has only been reported in three studies[2-4] in addition to a single case-report[5]. One study[2] examined 85 patients but applied only a single memory test and the methodology was not described in details. The remaining studies performed more extensive cognitive testing, but in contrast to our study were uncontrolled and included only respectively one, five and 10 patients[3-5] Prior studies were, in addition, based on patients with a wide range of disease duration (6-98 months) and only one study[3] reported ICP at time of testing. Our study is the first to assessed the cognitive function in a well-defined group of patients with newly diagnosed disease (n=29) or relapse (n=2).

While the case-study of Kaplan et al.[5] found no convincing cognitive deficits, Arseni et al.[2] and Kharkar et al.[4] reported substantial deficits in memory. We found deficits in visuospatial memory and in spatial working memory strategy, but detected no overall difference in working memory. Verbal memory (measured by Wecheler Memory Scale) was by far the most affected parameter in the study of Kharkar et al. and similarly was reported moderate to severe in 90% of the patients studied by Arseni et al. Although we did not test verbal memory we found significant deficits in other verbal functions (verbal fluency). This is in line with the study of Sorensen et al.[3] reporting verbal deficits in all of their five patients. Deficits in phonological fluency, which were substantial in our patients, have been shown to relate to frontal lobe damage, reflecting an additional executive component.[11]

The most severe deficits in our study were found in the domains of reaction time and processing speed which is consistent with the study of Sorensen et al.[3] In addition we found significant

impairment in cognitive flexibility. Cognitive flexibility is fundamental for effective decision-making and the ability to learn and adapt to environmental changes, but has never been tested in patients with IIH before.

Although overall working memory was not affected in our study, patients did score significantly worse in the working memory strategy. This may reflect an executive component consistent with other executive deficits detected in our patients.

The deficits we detected in the domains of reaction time, processing speed, visuospatial memory and attention were equivalent to those found in patients with first episode schizophrenia.[12] In addition deficits in cognitive flexibility were similar to those (measured by Wisconsin Card Sort, a task conceptionally akin to the Intra-Extra Dimensional Set Shift Test) found in a meta-analyses of patients with schizophrenia in general.[13] Verbal fluency in our patients was affected to the same extents as reported for patients with schizophrenia[13] as well as patients with congentital hydrocephalus.[11] Furthermore deficits in verbal phonological fluency and processing speed (measured by Symbol Digit Modalities Test) were in the range found in patients with multiple sclerosis.[14-16]

Despite marked improvement in ICP and headache we found no convincing signs of overall cognitive improvement at the 3- month follow-up as the improvement seen in the visuospatial tests could be explained by test-retest effect (familiarization with the Rey Ostereith Complex Figure). Sorensen et al.[3] reported that although signs of cognitive dysfunction were only minor, four of their five patients were unable to manage work and/or everyday activities. In our study 12 of the 31 patients were either on long-term sick-leave or had reduced and altered work schedule due to IIH at follow-up three months after diagnosis. Short follow-up and co-existent headache-symptoms limit the interpretation of the socioeconomic impact of cognitive dysfunction demonstrated in our study.

However, in other well recognized diseases such as schizophrenia a robust relationship between global and specific cognitive deficits and functional outcome has been consistently demonstrated.[17,18] The cause of cognitive impairment in IIH remains speculative. Theories could involve dysfunction of grey and/or white matter substance due to mechanical compression as proposed in normal pressure hydrocephalus,[11] dysfunction related to axonal flow as in optic nerve swelling and dysfunction[19] or release of cytotoxic substances as is seen in other conditions with cognitive decline.[20] To date there is no plausible evidence for brain damage in IIH[21] and as brain volume seems to be normal in IIH[22] we would expect any structural change that could explain the cognitive deficits found in this study to be subtle.

The strengths of the study is the prospective and controlled design, the broad range of cognitive tests, a relatively large study population, and the use of a culturally blind and computerized test battery that by automatic test conduction and score recording reduced the influence of the non-blinded observer. In addition the study population was well defined with cognitive testing performed in close relation to IIH diagnosis and ICP measurement. As patients were enrolled consecutively from both neurological and ophthalmological departments our study population reflects representative IIH-patients and not a selected group of cognitively symptomatic patients.

We recognize limitations to our study. First, the design was the non-blinded design and we did not perform retest of healthy controls. Secondly, the follow-up period was relatively short and may very well explain why we, unlike others,[3] failed to demonstrate improvement in cognitive function. Most importantly, although we adjusted for many of the most important confounders, our controls were not matched for BMI, headache or history of depression. The effect of headache on cognitive function has been debated,[23-25] but a recent comprehensive review concluded that there is no evidence of cognitive dysfunction in patients with migraine in general.[26] On the other hand there seems to be evidence that *chronic* pain is associated with mild cognitive impairment in selected

domains.[27,28] However, it is unclear if the cognitive impairment is attributed by the pain it self, or more likely mediated by co-existent depression.[29] Headache was chronic in 10 (32%) of our patients and depression was reported by eight (26%) patients. Neither depression nor chronic pain was associated with poorer cognitive performance when compared within the patient group. BMI in our patients ranged from normal to morbidly obese (24.2 – 48.8 kg/m^2). Patients with higher BMI did not perform worse than the less obese. Although it thus seems less likely that chronic pain, depression or obesity account for our findings of impaired cognition, sub-analyses were limited by small sample and statistical uncertainty. We acknowledge that to account for the influence of these potential confounders we ideally should have included an additional control group of obese patients with frequent headache. However, the vide range of factors potentially affecting performance in cognitive tests, and the great variation within the patient group, makes an ideal match very difficult to achieve. For future studies a feasible approach to this challenge could be to recruit subjects with suspected IIH, but in which the diagnosis is declined after appropriate investigations.

In conclusions, this study strongly suggests that IIH is associated with cognitive deficits. The results in addition indicate that the cognitive deficits are long-lasting, not paralleling ICP and headache reduction, and are not sufficiently treated by diuretics and weight loss. Contrary to our hypothesis executive and memory functions were only moderately affected. Nevertheless we found substantial deficits in processing speed and reaction time which could explain some of the difficulties that patients encounter in work and daily activities. A focused multidisciplinary approach including neuropsychological rehabilitation therefore might be relevant in the treatment of patients with IIH.

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COMPETING INTERESTS

H. Yri has received honoraria for consultant work from Neurocore and a travel grant from Berlin-Chemi Menarini. B. Fagerlund and H. Forchhammer report no disclosures. R. Jensen has received honoraria for lectures and patient leaflets from MSD, Berlin-Chemie Menarini, ATI and Pfizer and serves on medical advisory boards for LindeGas, ATI and Neurocore.

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AUTHOR CONTRIBUTION

HMY made a substantive intellectual contribute to the design of the study, acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript.

BF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

HBF made a substantive intellectual contribute to the design of the study, the interpretation of the data and the revision of the manuscript.

RHJ made a substantive intellectual contribute to the conceptualization and design of the study, the interpretation of the data and the revision of the manuscript.

DATA SHARING STATEMENT

No additional data are available

EXCLUSIVE LICENCE

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FIGURE TITLES AND LEGENDS

Figur 1.

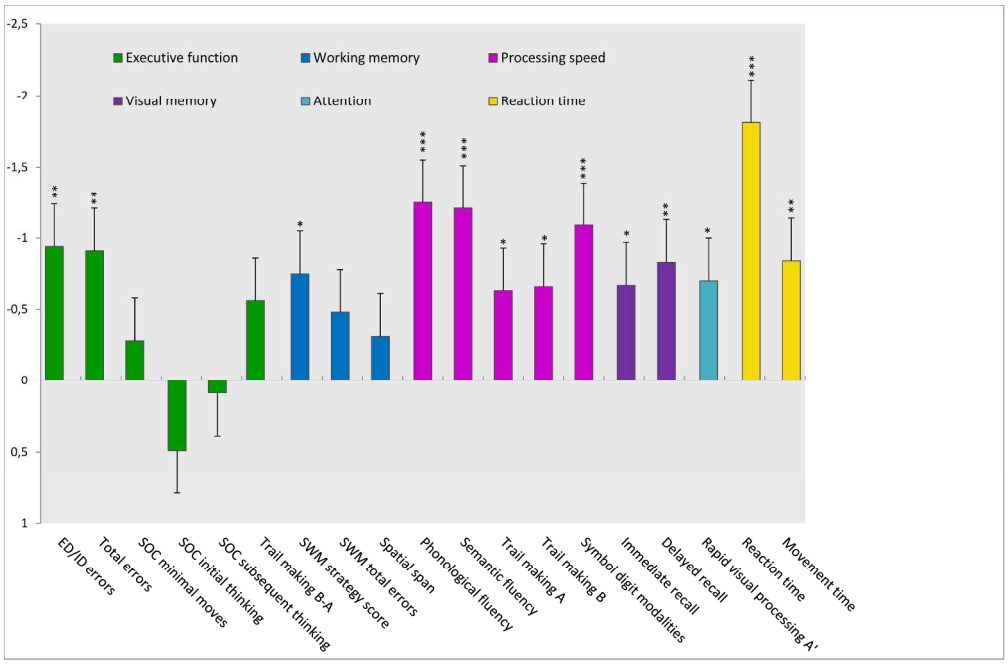
Title: Cognitive deficits in patients with IIH at time of diagnosis

Legends: Cognitive function in patients with IIH at time of diagnosis (n=31) shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. Colors indicate which domain the tests represent. *p<0.05 **p<0.005 ***p<0.0005.

Figure 2.

Title: Cognitive deficits in patients with IIH at time of diagnosis and at follow-up

Legends: Changes in test performance from time of diagnosis to follow-up (n=29) in patients with IIH shown in standard deviations from healthy controls (z-score). Error bars represent S.E.M. *p<0.05 **p<0.005 ***p<0.001.



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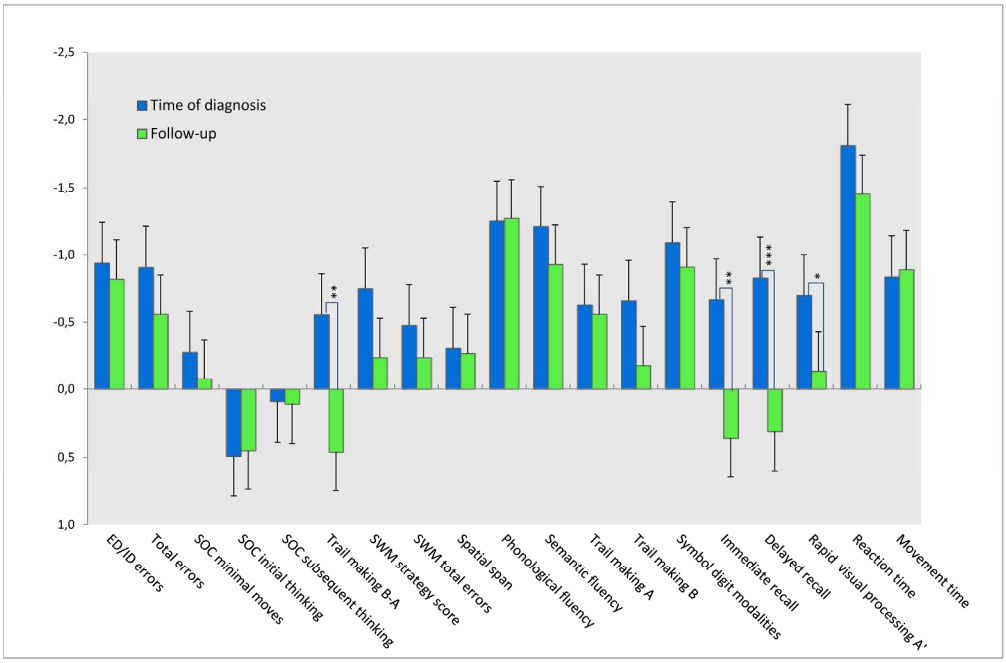

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Table 4. Differences in test performance between patients with and without chronic headache, patients with and without depression and the effect of BMI on test performance

	Chronic headache[a]			Depression[a]			BMI [b]		
	estimate	95% CI	P	estimate	95% CI	P	estimate	95% CI	p
Intra-Extra Dimensional Set Shift									
ID/ED Errors	-0.36	-1.26;0.54	0.43	0.05	-0.88;0.99	0.91	-0.02	-0.09;0.04	0.45
Total errors adjusted	0.09	-0.81;0.99	0.84	-0.13	-1.07;0.80	0.77	-0.01	-0.07;0.06	0.88
Stockings of Cambridge									
Solved in minimum moves	-0.10	-1.00;0.80	0.83	-0.42	-1.36;0.52	0.38	0.07	0.01;0.14	0.03[c]
Initial thinking time	0.25	-0.65;1.15	0.59	-0.32	-1.26;0.62	0.51	0.36	-0.04;0.10	0.36
Subsequent thinking time	0.37	-0.53;1.27	0.42	-0.14	-1.08;0.80	0.77	0.003	-0.06;0.07	0.92
Trail Making Test[a]									
Trail Making B-A	0.54	-0.39;1.46	0.25	0.52	-0.43;1.47	0.28	-0.04	-0.10;0.04	0.45
Spatial Working Memory									
Strategy score	0.31	-0.58;1.22	0.49	0.16	-0.78;1.09	0.74	0.02	-0.04;0.09	0.50
Total errors	0.57	-0.33;1.47	0.21	-0.07	-1.00;0.87	0.88	0.01	-0.06;0.07	0.87
Spatial Span:									
Span length	-0.51	-1.41;0.39	0.26	0.46	-0.48;1.40	0.33	-0.02	-0.08;0.05	0.64
Verbal Fluency[a]									
Letters	0.95	0.02;1.87	0.06	0.13	-0.82;1.08	0.78	0.01	-0.06;0.08	0.71
Categories	0.20	-0.72;1.13	0.67	-0.03	-0.98;0.92	0.95	0.003	-0.07;0.07	0.92

Trail Making Test[a]									
Trail Making A	0.64	-0.28;1.57	0.17	-0.19	-1.14;0.76	0.69	0.003	-0.07;0.07	0.94
Trail Making B	0.71	-0.21;1.64	0.13	0.33	-0.61;1.28	0.49	-0.02	-0.09;0.04	0.51
Symbol Digit Modalities									
Correct symbols	0.36	-0.54;1.26	0.43	0.28	-0.66;1.22	0.56	0.02	-0.05;0.08	0.61
Rey-Osterreith Figure									
Immediate recall	0.42	-0.48;1.32	0.36	-0.14	-1.07;0.80	0.78	0.02	-0.05;0.08	0.66
Delayed recall	0.67	-0.22;1.57	0.14	-0.04	-0.97;0.90	0.94	0.01	-0.06;0.07	0.87
Rapid Visual Processing									
A' sensitivity to target	0.49	-0.40;1.39	0.28	-0.26	-1.20;0.67	0.58	0.05	-0.02;0.12	0.15
Reaction Time:									
Reaction	0.49	-0.40;1.39	0.28	0.54	-0.40;1.48	0.26	0.02	-0.05;0.09	0.52
Movement	0.51	-0.39;1.41	0.27	0.27	-0.67;1.20	0.58	-0.01	-0.08;0.06	0.75

[a]Estimates are in SD and show difference between cognitive performance in patients without the dependent variable (depression and chronic headache) compared to patients with the variable. [b]Effect on test performance for every increasing BMI unit (kg/m^2). [c]Patients with higher BMI performed better. There was no significant difference between patients and controls in this test (Table 2).

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls page 4-5
		(*b*) For matched studies, give matching criteria and the number of controls per case page 4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6-7
Bias	9	Describe any efforts to address potential sources of bias page 7-8
Study size	10	Explain how the study size was arrived at page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions page 7-8
		(*c*) Explain how missing data were addressed page 7-8
		(*d*) If applicable, explain how matching of cases and controls was addressed page 5
		(*e*) Describe any sensitivity analyses not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10,14,15
		(b) Give reasons for non-participation at each stage page14
		(c) Consider use of a flow diagram not applied
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10-11
		(b) Indicate number of participants with missing data for each variable of interest page 11,13,16
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure page 10,14,15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10-16
		(*b*) Report category boundaries when continuous variables were categorized page 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 14
Discussion		
Key results	18	Summarise key results with reference to study objectives page 17-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 20
Generalisability	21	Discuss the generalisability (external validity) of the study results page 18-20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 21

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.