Neuropsychological Assessment in the Differential Diagnosis of Idiopathic Normal Pressure Hydrocephalus. An Important Tool for the Maintenance and Restoration of Neuronal and Neuropsychological Functions

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Abstract Idiopathic normal pressure hydrocephalus (iNPH) is a progressive clinical syndrome that includes gait disturbances, urinary incontinence, and cognitive impairment. iNPH shows similarities to other neurodegenerative disorders, primarily Alzheimer's Disease (AD). Definition of the neuropsychological profile of iNPH and the qualitative analysis of systematic mistakes made in cognitive tests could represent a valid method for systematizing possible specific markers of iNPH dementia and differentiating it from other dementias. To evaluate the role and the efficacy of a neuropsychological protocol, designed at our institution, based on psychometric analysis and qualitative assessment, in the differential diagnosis of iNPH from AD dementia, we prospectively enrolled 12 patients with suspected iNPH, 11 patients with AD, and 10 healthy controls (HC) who underwent neuropsychological assessment. The assessment was done with the Mini Mental State Examination (MMSE), Mental Deterioration Battery (MDB), Frontal Assessment Battery (FAB), and the Deux Barrage Test. Evaluation in the iNPH group was performed before extended lumbar drainage (ELD), 48 h after ELD, and 1 week and 3 months after the insertion of a ventriculoperitoneal shunt (VPS). Statistical analysis demonstrated the cognitive profile of iNPH, which was mainly characterized by executive function and immediate verbal memory impairment compared with AD. Additionally, the neuropsychological markers were different between the two groups. The qualitative analysis of systematic mistakes made on the tests demonstrated differences in cognitive performances between the iNPH, AD, and HC cohorts. Neuropsychological assessment and qualitative evaluation could represent a useful tool for achieving effective management and restoration of functions in patients with iNPH.

Keywords Idiopathic normal pressure hydrocephalus • Neuropsychological assessment • Qualitative analysis • Restoration

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) accounts for 2 %–10 % of all forms of dementia and 40 % of adult hydrocephalus [9]. The correct identification of iNPH, frequently hidden in the setting of coexisting diseases, and considering that 1 % of the population aged ≥65 years old shows ventriculomegaly without symptoms [10], is critical for maintaining neuronal and neuropsychological integrity and restoration [12]. However, the criteria used to select patients for treatment remain unclear [1]. The large amount of data that has emerged from recent series suggest that the cognitive profile of iNPH is a complex result of the impairment of several areas, which leads to specific alterations in executive functions, working memory, speed processing information, attention, learning and memory, and visuospatial functions, similar

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to the cognitive profile in Alzheimer's Disease (AD) [8, 9]. The modern concept of iNPH cognitive disorders is of a dysexecutive syndrome with episodic and immediate memory dysfunction [3, 5]. There is a lack of specific diagnostic criteria needed to systematically define neuropsychological markers that would be useful for achieving early diagnosis and outlining the specific neuropsychological profile of iNPH. The aim of this study was to evaluate the role and the efficacy of a neuropsychological protocol, designed at our institution, based on psychometric analysis and qualitative assessment, in the differential diagnosis of iNPH from AD dementia.

Materials and Methods

The Institutional Ethics Board of the University of Messina approved the study, and informed consent was obtained from each patient and/or their relatives. We prospectively enrolled 12 patients with clinically and neuroradiologically suspected iNPH. Inclusion criteria were: age ≥65 years, clinical triad (gait disturbances, dementia, and urinary incontinence), ventriculomegaly on magnetic resonance imaging (MRI), and other neuroradiological characteristics. Patients underwent a neuropsychological evaluation, with qualitative analysis to assess any systematic mistakes. Results were compared with those for 11 AD patients and 10 healthy controls (HC). The neuropsychological assessment was performed by C.S. and M.Q. (clinical neuropsychologists) on admission, 48 h after extended lumbar drainage (ELD) positioning, and postoperatively (1 week, and 1 and 3 months after VPS), when applicable. Patients who responded positively to preoperative tests for iNPH diagnosis were submitted to ventriculoperitoneal shunting with a programmable valve (Codman Hakim Medos; Codman & Shurtleff, Inc., 325 Paramount Drive, Raynham, MA 02767 0350, USA).

Neuropsychological Assessment

Quantitative Analysis The neuropsychological protocol adopted was chosen for its wide use in the neuropsychological community to assess dementia disorders, as it included several batteries for the assessment of general cognitive status, short- and long-term memory, episodic memory, immediate visual memory, constructive praxia, reasoning, and executive functions. The Mini Mental State Examination (MMSE), consisting of 30 items, allowed the exploration of temporospatial orientation, memory, attention, calculation, language (comprehension, repetition, denomination, reading, and writing), and constructive praxia. The highest score of 30 was modified in relation to age and education. The Mental Deterioration Battery (MDB) was divided into verbal and nonverbal tasks, including neuropsychological tests to detect the deterioration of different cognitive areas: memory, intellectual function, language, executive functions, and constructive praxia. The MDB included seven subtests for immediate and delayed recall, the Rey Auditory Verbal Learning Test (RAVLT), for evaluating semantic and phonological fluency, phrase construction, and immediate visual memory; and Raven's Colored Progressive Matrices test (PM 47), which involves copy drawings, and copy drawings with landmarks. The Deux Barrage Test was used to evaluate divided attention. The Frontal Assessment Battery (FAB) enabled the assessment of executive functions.

Qualitative Analysis In order to distinguish between cognitive impairments in iNPH and AD, we employed the following markers for AD diagnosis: in RAVLT, the absence of the primacy effect derived from a verbal learning task, the presence of the recency effect, the absolute decay of memory trace, and the tendency to produce false alarms during delayed recognition of the same word list; in Raven's Colored Progressive Matrices test, the tendency to choose globalistic or odd responses and positional preference mistakes; in the copy drawings test, the occurrence of the closing-in phenomenon; and in the Deux Barrage Test, inaccuracy in task execution. When the abovementioned markers were mostly presented, we were able to confirm the AD diagnosis, and to exclude those clinically suspected of having iNPH.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism Software (GraphPad Software, Inc., La Jolla, CA 92037, USA). For the descriptive analysis of neuropsychological scores we used nonparametric analysis of variance (ANOVA); we used the Fisher test to compare the frequencies of systematic mistakes in iNPH and AD patients and the paired Student's *t*-test to evaluate the effect of ventriculoperitoneal shunting on cognitive functions in iNPH patients. Additionally, we used the SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL,

USA) [23] to evaluate the covariance of cognitive functions in iNPH patients following surgical treatment. $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics We prospectively enrolled 12 patients (8 male; 4 female) with suspected iNPH; mean age 70 ± 6 years, mean educational level 9 ± 4 years. In order to compare psychometric results and systematic mistakes, we also enrolled 11 patients (7 male; 4 female) with AD; mean age 76 ± 5 years, mean educational level 8 ± 5 years; and 10 HC volunteers (4 male; 6 female), mean age 72 ± 8 years, mean educational level 11 ± 5 years. Seven iNPH patients who responded positively to preliminary tests, underwent ventriculoperitoneal (VP) shunting within 2 weeks after assessment.

Quantitative Results Table 1 summarizes the mean ± standard deviation values and statistics of the neuropsychological scores for the iNPH, AD, and HC groups on admission. As compared with the HC group, iNPH and AD patients showed significant impairments of different cognitive functions, including MMSE, short- and long-term memory (RAVLT), reasoning (PM 47), and semantic and verbal fluency, language, and constructive praxia. AD patients showed impairments of episodic memory, immediate visual memory, and executive functions. The ANOVA showed statistically significant differences between the iNPH and AD groups in MMSE, long-term memory, episodic memory, immediate visual memory, language, constructive praxia, and executive functions. Table 2 shows the frequencies of different mistakes in the iNPH and AD patients. The iNPH patients presented significant differences, compared with the AD group, in primacy effect, tendency to produce false alarms during delayed recognition of words, globalistic responses, odd responses, inaccuracy on the Deux Barrage Test, and the occurrence of the closing-in phenomenon. Table 3 shows the effect of VP shunting on cognitive performances. In detail, we observed a significant improvement in short- and long-term memory, immediate visual memory, and reasoning in these patients.

Correlational Analysis When performing the correlational analysis of the neuropsychological scores, we did not find significant differences between the cognitive profiles of iNPH and AD patients. In the AD group the correlation coefficient showed a statistically significant between general

Table 1 Summary of the neuropsychological scores in iNPH, AD, and HC groups on admission

	iNPH	AD	HC	Cutoff
Neuropsychological assessment				
Mini Mental State Examination	18.8 (±6.7) ** ###	16.5(±4) ****	27(±2)	0–30
Mental assessment battery				
RAVLT immediate	25.8 (±5) **	22.4(±5) ****	39 (±9.3)	>28.53
RAVLT delayed	4.87(±2.4) *** #	3(±2) ****	10(±2)	>4.69
RAVLT recognition	9(±2)	6(±3)	13.4(±1.5)	0–15
Episodic memory	8(±3) #	4.6(±2.2) **	11(±4.4)	0–28
Immediate visual memory	15.7(±2.7) ##	12.6(±4.6) ***	19(±3)	0–22
Raven's Colored Progressive Matrices	18(±5.4) *	16(±6.4) ***	27(±5.3)	>18.96
Semantic verbal fluency	11. 3(±3) *	9.3(±3.5) ***	18(±5)	>7.25
Phonological verbal fluency	18.3(±12) **	17.2(±10) **	35.3(±9.4)	>17.35
Phrase construction	13.7(±8) ** ##	5(±5) ****	23(±3)	0–25
Copy drawing	5.5(±3) * #	4(±2.7) ***	9.3(±1.2)	>7.17
Copy drawing with landmarks	54.5(±7.2) **	35.3(±26) ***	66.5(±4)	>61.85
Frontal Assessment Battery	9(±4) #	9(±5.6) *	14(±3.4)	>12.03

Data are presented as means ± SD

iNPH idiopathic normal pressure hydrocephalus, *AD* Alzheimer's Disease, *HC* healthy control, *RAVLT* Rey Auditory Verbal Learning Test

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.005$, **** = $p < 0.0001$ when comparing iNPH and AD vs HC, # = $p < 0.05$, ## = $p < 0.01$, ### = $p < 0.005$ when comparing iNPH vs AD

Table 2 Frequencies of different mistakes in iNPH and AD patients

	iNPH	AD	Fisher test
Primacy effect	10	2	$p=0.03$
Recency effect	10	10	–
Tendency to produce intrusions during free recall of words	10	24	–
Tendency to produce false alarms during delayed recognition of words	21	95	$p=0.001$
Globalistic responses	0	22	$p=0.0003$
Odd responses	4	42	$p=0.01$
Positional preference responses	134	53	–
Inaccuracy on the Deux Barrage test	1	8	$p=0.0001$
Occurrence of closing-in phenomenon	1	53	$p=0.001$

Table 3 Neuropsychological performance in 12 iNPH patients on admission, and after surgical treatment in 7 patients

iNPH	Pre ELD	Post ELD	Post VPS	Post 1 month	Post 3 months	Cutoff
Neuropsychological assessment						
Mini Mental State Examination	18.8(±6.7)	23.5 (±3.3)	24(±3)	24(±3)	25.4(±4)	0–30
Mental assessment battery						
RAVLT immediate	25.8 (±5)	30.3 (±5)	39(±13) *	42.3(±16.5) #	40(±19)	>28.53
RAVLT delayed	4.8(±2.4)	5.5(±2.4)	8(±4.5)	8(±3.5) ##	6(±4.2)	>4.69
RAVLT recognition	9(±2)	12.3(±3)	13.6(±1.5)	12.2(±3)	12.4(±3)	0–15
Episodic memory	8(±3)	9(±0.8)	11(±5.4)	12(±6)	18.2(±12.4)	0–28
Immediate visual memory	15.7(±2.7)	16(±3)	19(±2) *	19.4(±1.5)	20(±1.3)	0–22
Raven's Colored Progressive Matrices	18(±5.4)	24(±3)	24.4(±7)	26(±4) #	27.5(±3)	>18.96
Semantic verbal fluency	11(±3.3)	10.5(±3)	23(±20)	13(±4.7)	15.4(±6)	>7.25
Phonological verbal fluency	18.3(±12)	18.6(±11.5)	17.5(±13)	20.4(±16)	19(±12)	>17.35
Phrase construction	13.7(±8)	11.2(±2.5)	18.6(±7.5)	18(±6)	20.3(±9)	0–25
Copy drawing	5.5(±3)	6.2(±4)	8(±4.3)	9(±2)	6(±2)	>7.17
Copy drawing with landmarks	54.5(±7.2)	55(±19.4)	63(±9)	63(±8)	61(±5)	>61.85
Frontal Assessment Battery	9(±4)	10.5(±2.6)	11(±5)	9(±3.5)	13(±2)	>12.03

Data are presented as mean ± SD

Pre ELD: pre external lumbar drainage, *Post ELD*: post external lumbar drainage, *Post VPS*: post ventriculoperitoneal shunt

* = $p<0.05$ when comparing pre- and 1 week postoperative performances, # = $p<0.05$, ## = $p<0.01$, when comparing pre- and 1-month postoperative performance

cognitive dysfunction, memory, praxia, and executive function impairment (*rho 0.814;* $p<0.01$). As compared with AD patients, the iNPH group showed a significant association between executive variables and memory abilities (*rho 0.798;* $p<0.05$). In the iNPH group, we observed a significant cognitive improvement after ELD in immediate verbal memory and semantic phonological verbal fluency (*rho 0.829;* $p<0.05$), and in divided attention and praxia (*rho 0.926*; $p<0.01$). The improvement of immediate verbal memory, as assessed 1 week postoperatively, was significantly related to delayed verbal memory (*rho 0.900;* $p<0.05$).

Discussion

In the present study we assessed the role of a neuropsychological protocol, combined with the qualitative analysis of systematic neuropsychological mistakes, in the differential diagnosis of iNPH from AD, as compared with results in the HC group. For this purpose we employed specific markers to exclude the AD syndrome, and we evaluated the frequencies of these markers in the iNPH patients. Moreover, the effect of surgery on postoperative cognitive neuropsychological restoration was evaluated. We have demonstrated that the psychometric tests cannot be considered as a sufficient tool for differentiating AD from iNPH patients. Conversely, the combination of neuropsychological markers and psychometric tests was able to achieve an effective differential diagnosis between iNPH and AD.

iNPH represents a complex syndrome for which several authors have attempted to systematize criteria, in order to obtain an effective differential diagnosis from other neurodegenerative disorders or comorbidities [7, 11, 16–19]. iNPH, and its neuropsychological profile, are, to date, still not clarified [6, 8, 14, 20], and a detailed characterization of the cognitive dysfunction in iNPH, especially in view of the specific neuropsychological patterns and differentiation of iNPH from AD, is crucial both for a correct diagnosis [4, 15, 21] and for obtaining neuropsychological restoration following treatment [2, 4, 22]. The neurocognitive profile of patients with suspected iNPH was mainly characterized by the impairment of executive functions and short-term memory [13], whereas in AD patients, the neurocognitive profile was mainly characterized by alterations of general cognitive status, short- and long-term memory, praxia, and executive functions. In detail, we found significant differences between the iNPH and AD groups in MMSE, long-term memory, episodic memory, immediate visual memory, language, constructive praxia, and executive functions. The qualitative analysis of systematic mistakes, made during the assessment, demonstrated statistically significant differences between our groups. iNPH differed from AD patients in the following markers: primacy effect, tendency to produce false alarms during delayed recognition of words, globalistic responses, odd responses, inaccuracy on the Deux Barrage, and the occurrence of the closing-in phenomenon. As compared with results in AD patients, scores in iNPH patients showed a significant association with executive variables and memory abilities. Changes in neuropsychological performances were demonstrated after ELD, 1 week after the operation, and at 1 and 3 months postoperatively.

The results of the present study are not unexpected, and are in line with those already published in the literature [6, 8]. We recognize that the limited series in the present study does not allow us to draw definitive conclusions. However, the neuropsychological assessment based on psychometric scores and qualitative analysis of neuropsychological patterns may represent a useful tool for making a correct differential diagnosis between iNPH and AD, and for achieving the restoration of neuronal and neuropsychological functions after treatment. These results may encourage an extension in the use of such a protocol to define the cognitive profile of iNPH.

Conflict of Interest Statement The authors declare that they have no conflict of interest.

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