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Article

Idiopathic normal pressure hydrocephalus diagnosis: quantitative and qualitative score predicting outcome of extended lumbar drainage

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Abstract: Background: Idiopathic normal pressure hydrocephalus is a syndrome with neuroradiological findings and clinical pattern characteristic but not specific for the pathology. Since the prevalence is growing due to the rapidly aging society, standardized and validated protocol for diagnosis is needed, also because this condition may mimic other disorders among elderly such as Parkinson's and Alzheimer's disease. **Material and methods**: We analysed data from 44 patients with suspect diagnosis of idiopathic normal pressure hydrocephalus with age > 60 years, clinical triad and neuroradiological pattern examined in our ward from November 2018 to November 2022. Neuropsychological assessment includes Mini Mental State Examination and Mental Deterioration Battery. Motor scores were collected from gait and balance tests. The evaluation was performed before and after an extended lumbar drainage last 48h. Patients who has scores improvement after the extended lumbar drainage, undergo ventriculoperitoneal shunt with a programmable valve. **Results**: All patients undergo neuropsychological assessment and motor tests, only 2 patients were unable to perform motor tests because bedridden. 16 patients showed no benefit from the tests, in 2 cases even a worsening of cognitive performance. 28 patients showed an improvement in their performances, but in most cases the improvement involved only the neuropsychological assessment. All patients underwent ventriculoperitoneal shunt have had a typical answers pattern in Mental Deterioration Battery test. We performed 9 ventriculoperitoneal shunt and 1 ventriculo-atrial shunt. **Conclusions**: Qualitative neurocognitive tests come out to be more sensitive compared to quantitative neurocognitive tests in identifying patients with suspected idiopathic normal pressure hydrocephalus benefiting from extended lumbar drainage test and then underwent surgical treatment. This could be considered a valid screening in elderly patients with suspected idiopathic normal pressure hydrocephalus in order to minimize the number of invasive procedures. More studies are necessary to validate this tool.

Keywords: Extended lumbar drainage; Hydrocephalus; Idiopathic normal pressure hydrocephalus; neurodegenerative diseases; Qualitative neurocognitive tests; Quantitative neurocognitive tests;

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a neurologic disorder first described by Hakim and Adams in 1965 in a case series in which patients presented the characteristic triadic syndrome (gait disturbances, cognitive impairment and urinary incontinence) along with ventriculomegaly and cerebrospinal fluid (CSF) pressure within the normal range[1]. This condition was defined as idiopathic NPH due to its unknown origin contrary to secondary NPH caused by other neurological injury (e.g., subarachnoid or cerebral haemorrhage, meningitis). The cause of iNPH ventricular expansion has not been fully investigated. An impairment in the absorption of CSF or an imbalance between its production and absorption is hypothesized. iNPH is not a rare clinical entity. The prevalence is growing due to rapidly aging society and has been estimated to be 10 per 100 000 to 22 per 100 000 overall, with 1.30% in those aged ≥65 years and 5.9% in those aged ≥80 years[2]. It manifests after the 6th decade with neuro-radiological typical findings (ventriculomegaly, sylvian fissure dilation, narrowing of the high convexity/midline subarachnoid spaces, steepening of callosal angle)[3] in combination with the clinical Hakim-Adam's triad. Treatment by placement of ventriculo-peritoneal shunt (VPS) and ventriculo-atrial shunt (VAS) is successful in reversing symptoms in more than 80% of the patients[4].

To date, several tests are used for the diagnosis of iNPH and the prediction of a favourable outcome following shunt placement. Those tests include both motor tests that analyse the patient's balance and coordination and neuropsychological assessment aimed at identifying a typical pattern of patients with iNPH that can be distinguishable from other forms of dementia. iNPH grading scale (iNPHGS)[5] is a subjective scale that evaluates gait disturbance, cognitive impairment, and urinary incontinence on a scale from 0 to 4, adapting the scale to patients with a wide range of symptom severity. The total score can be used as an index, together with the evaluation points for each of the three conditions. The iNPHGS is used along with other objective and quantitative evaluation methods as the timed up & go test (TUG)[6] a valid test for evaluating walking ability in which the time required to pass from sitting to standing position and to walk forward 3 m and return to the seated position with no physical assistance is calculated. In this test if the patient was at risk of falling, the examiner followed him a half-step behind to prevent a fall without affecting the patients' walking pace.

iNPH cognitive impairments have been described as fronto-subcortical dementia[7,8], but the term is reductive as it does not fully describe the different clinical pictures observed[9]-[10]. In the early stages, the cognitive profile is characterized mainly by impairments of attention, psychomotor speed and memory. Memory impairment is characterized by difficulty acquiring new information and retrieving it. Patients with more advanced iNPH show overall cognitive deteriorate, with consequent specific alterations in executive functions, memory, working memory, information processing speed, attention, memory, visuospatial and visuo-constructional skills, psychomotor slowing and mood symptoms, especially apathy. However, iNPH symptoms are nonspecific and frequently found in other neurological disorders. The characteristics of cognitive decline in patients with iNPH can be varied, in some cases it can be similar to normal aging, in others it can manifest itself as progressive dementia with impaired gait comparable to Alzheimer's (AD) or Parkinson's disease[11]-[12]. The diagnosis and criteria used to determine which patients to treat are still unclear. 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. For cognitive assessment are recommended the Mini-Mental State Examination (MMSE), the Wechsler Adult Intelligence Scale-III digit symbol coding and symbol search tasks and the Frontal Assessment Battery. The Rivermead Behavioral Memory Test, a parallel test, is a recommended memory test. Emerges the need to improve the diagnostic procedure to identify the appropriate candidates for surgery compared to patients with neurological disorders comparable to iNPH, but who would not obtain symptomatic reversibility from the surgical procedure. A large part of the literature has focused on an analysis of quantitative differences between different cognitive domains and between pre and post CSF drainage. Through this study we tried to examine the qualitative differences between iNPH and other neuropsychological disease in order to identify and differentiate the possible neuropsychological markers as an aid in the diagnostic procedure.

2. Materials and Methods

Participants

We retrospectively analysed data of 44 consecutive patients with suspected iNPH admitted to the Neurosurgery Unit of the University Hospital "G. Martino" of Messina, from November 2018 to November 2022. Inclusion criteria were age ≥65 years, clinical triad (gait disturbances, dementia, and urinary incontinence), ventriculomegaly on magnetic resonance imaging (MRI). Age, gender, years of education were collected (Table 1). The exclusion criterion was the presence of ventriculomegaly secondary to other pathological condition. All patients underwent neuropsychological assessment with MMSE and Mental Deterioration Battery (MDB) and they were videotaped for gait and balance analysis prior to and 2 h following ELD last 48 hours. Only two patients did not undergo motor tests due to bedridden. On the basis of improvement of cognitive and motor performances post ELD, patients were divided into two subgroups, iNPH and non-iNPH patients. Only 10 patients of iNPH group were submitted to surgical treatment (ventriculo-peritoneal or ventruculo-atrial shunting with a programmable valve). Informed consent was obtained.

Table 1. 44 patients included in the study. The table show age (≥65 years), gender, years of education (YoE), clinical triad (cognitive disfunction, gait disturbances and urinary incontinence). Motor and NPS tests were performed. Improvement column shows the NPS evaluation after ELD: (-) no improvement; (+) not significant improvement; (++) significant improvement. X: present/performed; NE: not executable; VPS: ventriculo-peritoneal shunt; VAS: ventriculo-atrial shunt.

Patients	Age	Gender	YoE	Clinical triad	Motor test	NPS test	Improvement	Surgery
1	67	M	5	X	X	X	-	
2	74	M	5	X	X	X	++	VPS
3	74	M	8	X	X	X	+	
4	78	F	18	X	X	X	-	
5	80	M	8	X	X	X	+	VPS
6	80	M	18	X	X	X	++	VPS
7	69	M	5	X	X	X	++	VAS
8	80	M	18	X	NE	X	++	
9	68	M	13	X	X	X	+	VPS
10	75	M	8	X	X	X	+	
11	72	M	13	X	X	X	-	
12	71	M	2	X	X	X	+	VPS
13	69	F	8	X	X	X	++	
14	75	F	8	X	X	X	++	
15	60	F	13	X	X	X	-	
16	72	F	18	X	X	X	+	
17	71	M	5	X	X	X	++	VPS
18	69	M	13	X	X	X	+	
19	63	M	8	X	X	X	+	VPS
20	83	M	5	X	X	X	++	
21	71	F	5	X	X	X	+	
22	73	F	18	X	X	X	-	
23	69	M	13	X	X	X	++	VPS
24	81	M	5	X	X	X	++	VPS
25	63	M	13	X	X	X	++	
26	64	F	18	X	NE	X	-	

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27	67	M	8	X	X	X	-
28	67	F	5	X	X	X	-
29	49	F	8	X	X	X	-
30	62	F	13	X	X	X	++
31	68	F	13	X	X	X	++
32	68	M	8	X	X	X	++
33	72	M	8	X	X	X	-
34	68	M	8	X	X	X	-
35	78	M	8	X	X	X	++
36	78	M	18	X	X	X	++
37	75	F	5	X	X	X	+
38	78	F	5	X	X	X	-
39	68	F	13	X	X	X	-
40	84	M	18	X	X	X	-
41	74	F	4	X	X	X	+
42	81	M	13	X	X	X	-
43	67	F	13	X	X	X	+
44	75	F	5	X	X	X	-

Neuropsychological Assessment

The protocol we have chosen includes several tests widely used in the neuropsychological community for the evaluation of cognitive impairment.

The MMSE[13] is a quantitative test that consists of 30 items and investigates that space-time orientation, memory, attention, calculation skills, language, in the sub-components comprehension, repetition, naming, reading and writing and praxic-constructive abilities. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The raw score, whose cutoff is 25, is corrected for age and education.

The MBD[14] test consists of 8 sub-tests, verbal and non-verbal, which have proven to be sensitive and valid in detecting the presence of cognitive impairment in different areas. Specifically includes:

1) Rey Auditory Verbal Learning Test (RAVLT), for assessing immediate and deferred learning of new information. It is administered by reading the list of words to the patient, at the speed of one word per second with no inflection of the voice until the end of the list. At the end of the reading, the patient is asked to repeat as many of the words just heard as possible in any order. This procedure is used, with the same list of words five consecutive times, recording each time different elements not only quantitative but also qualitative (immediate recall). After an interval of 15 minutes, during which visuo-spatial tests are performed, the patient is asked to remember (without the list being re-proposed by the examiner) as many words as possible from the list (deferred recall);

2) Raven's Colored Progressive Matrices, PM 47 for the assessment of logical-deductive intellectual abilities. This test is particularly suitable for studying the entire range of intellectual functions and, requiring minimal verbal and motor expressions, is particularly suitable for studying normal or pathological ageing. The test consists of 36 matrices divided into 3 sets (A-AB-B), 12 items each. Each item requires you to identify, among 6 alternatives, the piece that completes the matrix. The test is administered without time limits. One point is awarded for each correct answer. The raw score, given by the sum of

the correct answers, is corrected for age and education. The cutoff for normality purposes is equal to 18,96;

3) Immediate Visual Memory Test, for evaluating the visuo-spatial working memory for a visual stimulus (PM 47 tiles). It consists of 22 items made up of single cards that the subject must memorize in three seconds, then the second table is presented which contains 4 cards vertically aligned, including the one just presented that the patient must recognize. One point is awarded for each correct answer. The raw score is adjusted for age and education and the cutoff is 13,85;

4) Phonological Fluency Test, for the assessment of access and lexical retrieval. Subjects are asked to say as quickly as possible the largest number of words that come to mind and begin with a specific letter (F; A; S). the required time is 1 minute. One point is awarded for each correct word. The raw score, given by the sum of the words produced for the three categories, is corrected for age and education. The cutoff for normality purposes is 17,35;

5) Semantic Fluency Test, for evaluating the extension and usability of the vocabulary. Subjects are asked to say as quickly as possible the largest number of words that come to mind from a specific category of meaning (colors; animals; fruit; city). The time required for each category is 2 minutes. One point is awarded for each correct word. The raw score, given by the sum of the words produced for the four categories, is corrected for age and education. The cutoff for normality purposes is 7,25;

6) Copy Drawings, for the assessment of praxico-constructive ability and consists of free-hand copying of 3 items, one two-dimensional and two three-dimensional (star; cube; house). For each item a score of 4 is assigned if the perspective, the orientation of the lines, the spatial relationship and the proportion between the parts are correctly reproduced; 3 if the drawing is clearly recognizable and all the constituent elements are present and correctly positioned; however, perspective is lost and/or there are slight imperfections regarding the orientation of the lines, the spatial relationship or the proportion between the parts; 2 if the drawing is difficult to recognize due to the lack, or the dislocation, of one or more constituent elements and/or due to serious imperfections in the orientation of the lines, in the spatial relationship or in the proportion between the parts; 1 point if the drawing is not recognizable, but the phenomenon of assignment to the model is not observed; 0 points if the closing-in phenomenon is present. The raw score is corrected for age and education and the cutoff for normality purposes is 7,18;

7) Copy Drawings with Landmarks, for the evaluation of the praxico-constructive ability starting from programming elements. For each figure, 1 point is awarded for each completed line, incorrect graphic strokes are not counted for the purposes of the score, corrected for age and schooling. The cut-off for normality purposes is 61,85;

8) Phrases Construction, for evaluating the ability to relate lexical units in a coherent syntactic construct. Stimulus words are provided for the construction of meaningful sentences. The cutoff is 8,72 after correction for age and education.

Babcocks Story (BS)[15], immediate and deferred recall, for the evaluation of episodic memory. The test also involves mechanisms for integrating the information that is provided to enable verbal comprehension and subsequently involves planning mechanisms for the structure of the stored information to be repeated consistently. the score is given by the average of the number of elements recalled in the two repetitions in a range from 0 to 28. The cutoff for normality purposes is < -7,5.

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Deux Barrage Test[16], for the evaluation of divided attention. A sheet with 40 lines of signs is presented, among which there is one, specified at the beginning, that the subject must cross out. the score given is given by the combination of exact, omitted and incorrect elements.

Gait and Balance Assessment

Gait assessment includes the 10 m-walking test that consists in the measurements of the number of steps and seconds needed to walk 10 m at free pace, in a straight line as soon as possible. Measurements begin from a stationary position. If the patient has a walking aid, he should use it. The test is repeated two times and mean values are considered. For balance evaluation a 360° turn test was conducted, during which the number of steps needed to complete the turn was recorded. The mean of two turning trials was then calculated. The number of seconds in which the patient can stand up straight on one or both legs and the capacity and number of seconds it takes to sit down and stand up are calculated. After consent all patient's performances were videotaped.

ELD test

We performed ELD test due to high positive predictive value (PPV) and high negative predictive value (NPV) compared to simple lumbar puncture (LP). Before the procedure, complete blood test including platelet count, prothrombin time and partial thromboplastin time were obtained. Patients must have stopped anticoagulant medications and all tests needed to be within normal limits. All patients were given a prophylactic dose of intravenous antibiotic (cephazolin or vancomycin if allergic to penicillin) before the drain placement. Patients have to maintain lateral decubitus or sitting position in order to flex the spine better. With a sterile technique and after infiltration with lidocaine, a 8-gauge Tuohy needle was used to access the subarachnoid space in the vertebral interspace between L3-L4 and L5-S1. When CSF was observed, 10-15 cm of a 90-cm long and 20 gauge catheter was inserted through the Tuohy needle into the subarachnoid space. The drain was secured to the skin of the back and the catheter was connected to an external CSF collection bag. The drainage is held for 48 hours and then it is removed.

Statistical analysis

Statistical analysis was performed with SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA). For the descriptive analysis of neuropsychological score we used nonparametric analysis of variance (ANOVA); Fisher test was used 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. $p < 0.05$ was considered statistically significant.

3. Results

We retrospectively analysed data of 44 consecutive patients (26 males, 18 females; mean age = 71.6 ± 6.8). All patients underwent brain CT, MRI and neurological examination. The average years of education is 10.9 ± 4.9. All patients underwent neuropsychological assessment with MMSE and MDB and they were videotaped for gait and balance analysis prior to and 2 h following EDL lasted 48 hours. In 10 patients the preliminary tests suggested indication to surgery. About 4 weeks after the assessments, VPS was performed in 9 cases and VAS in 1 case, all of them with a programmable valve set at a pressure of 140 mmH_2O. In the postoperative period, we did not observe complications related to the surgical procedure. The neuroradiological examinations performed (CT scan performed 6 days after the surgical procedure, MRI performed 30 days after the surgical procedure) showed the correct positioning of the ventricular catheter in the absence of complications. The volumetric dimensions of the ventricular system appeared slightly decreased. The remain 18 patients, with significant improvement in symptoms and cognitive performances after ELD, did not undergo surgery due to comorbidities or because they refuse it.

Quantitative Analysis

Patients were assessed before and after ELD.

Assessment pre-ELD of iNPH group (n. 28) shown impairment of short- and long-term memory (RAVLT), praxico-constructive abilities (TC and TCEP), phonological fluency (WFF), and divided attention (DEUX BARRAGE). The ELD procedure affects positively the cognitive performances of this group more than non-iNPH patients (Table 2).

ANOVA demonstrated a significant improvement in 16 patients among the 28 of iNPH group. Specifically, both short- and long-term mnemonic skills significantly improved in the episodic component, reasoning, praxico-constructive skills, word fluency and divided attention. The remaining 12 patients of iNPH group, despite improvement post ELD, ANOVA did not demonstrate significant changes.

In a further subset of 16 patients (non-INPH group) ELD produced no benefits. In this group, the neuro-psychological evaluation on admission to the ward had recorded a greater impairment of global cognitive functioning compared to iNPH patients (Table 3). This finding was confirmed by ANOVA.

Table 2.

Neuropsychological assessment	iNPH				non-iNPH			
	N	pre EDL	post EDL	*p-value*	N	pre EDL	post EDL	*p-value*
MMSE	28	21,17 ±5,13	24,22 ±3,86	**,001***	16	16,78 ±5,33	16,62 ±4,02	,813
Metal Deterioration Battery								
RAVLT immediate	28	26,09±9,6	29,95±9,15	**,008***	16	19,12±6,09	17,04±5,23	**,041***
RAVLT delayed	28	4,7±2,65	5,77±2,78	**,013***	16	3,3±1,79	2,57±1,01	,054
PM 47	28	20,91±5,42	23,61±4,44	**,001***	16	15,34±7,54	12,71±8,46	**,015***
IVM	28	14,89±3,95	18,21±2,87	**,000***	13	14,07±4,53	12±5	**,005***
Phonological fluency	28	16,82±5,93	17,94±5,97	,154	11	13,05±5,48	10,2±4,55	**,012***
Semantic fluency	28	8,95±2,7	10,3±3,27	**,000***	11	6,67±3,55	4,04±2,87	**,036***
TC	28	7,62±2,74	8,54±2,06	,053	11	5,05±2,90	4,18±3,16	,099
TCEP	28	56,1±15,55	59,84±12,45	,114	11	41,74±23,99	25,93±27,4	**,042***
Phrase construction	28	18,52±7,20	20,38±6,89	**,009***	11	10,3±6,17	10,49±7,09	,880
Episodic memory	28	9,64±3,87	12,85±4,79	**,000***	11	7,72±5,18	6,45±4,44	,068
Deux barrage	28	6,92±3,69	8,68±4,27	**,024***	11	5,5±5,25	2,06±3,42	**,036***

Table 3. Summery of the neuropsychological assessment in iNPH and non-iNPH groups on admission.

Neuropsychological assessment pre EDL	iNPH	non-iNPH	*p-value*	Cutoff
MMSE	21,17 ±5,13	16,78 ±5,33	**,010***	25
Metal Deterioration Battery				
RAVLT immediate	26,09 ±9,6	19,12 ±6,09	**,012***	28,53
RAVLT delayed	4,7 ±2,65	3,3 ±1,01	,068	4,69
PM 47	20,91 ±5,42	15,34 ±7,54	**,007***	18,46
IVM	14,89 ±3,95	14,07 ±4,53	,359	13,85
Phonological fluency	16,82 ±5,93	13,05 ±5,48	**,015***	17,35
Semantic fluency	8,95 ±2,7	6,68 ±3,55	**,029***	7,25
TC	7,62 ±2,74	5,05 ±2,9	**,001***	7,18
TCEP	56,1 ±15,55	41,74 ±23,99	**,001***	61,85
Phrase construction	18,52 ±7,20	10,3 ±6,17	**,002***	8,72
Episodic memory	9,64 ±3,87	7,72 ±5,18	,080	7,5
Deux barrage	6,92 ±3,69	2,06 ±3,42	,125	

Qualitative Analysis

This study was conducted to analyze the utility of cognitive impairment tests as screening marker between iNPH group and non-iNPH. The frequency of systematic errors differs significantly between the groups: patients identified as iNPH show a significant tendency to give orientation misdirection stimulus responses to the PM47 test, while non-iNPH group show a significant tendency to give global misresponses stimulus responses in the same task. The CT closing-in effect is another erroneous response that distinguishes iNPH patients from non-iNPH patients (Table 4).

Table 4. Systematic errors frequencies of qualitative tests between iNPH and non-iNPH.

Frequencies of systematic errors	iNPH	non-iNPH	Fisher test (p-value)
Primacy effect	21	8	,111
Recensy effect	28	15	,363
Globalistic responses	3	12	**,000***
Orientation responses	28	9	**,0003***
Closing-in	0	8	**,000***

4. Discussion

iNPH is a complex syndrome that typically occurs in the elderly population who also has other comorbidities. Several neurodegenerative diseases can mimic iNPH and, this heterogeneity makes diagnosis challenging. To date, both instrumental neuroradiological examinations (CT scan, MRI) and neuropsychological examinations are unable to establish the correct diagnosis between iNPH or other forms of neurodegenerative diseases.

Neuroradiological features

MRI is the first-choice test. MRI allows to evaluate the degree and location of the dilatation of the ventricular system, and it can allow to exclude or confirm the presence of expansive lesions, or malformations, and to evaluate the dimensions of the ventricular system, specifying the extent of the dilatation and identifying the compartments of the CSF pathways involved (Figure 1). It also provides indirect data on the severity of hypertension in the form of a more or less extensive periventricular streak, defined as transependymal absorption (Figure 2). MRI also provides information on CSF flow in the various districts. In fact, the signal intensity of the CSF reflects its speed, being lower in the points with the highest flow speed (Figure 3). The features in a radiological examination are the enlargement of the ventricular system in the absence of an obstruction; therefore, a fundamental prerequisite is the presence of a tetraventricular system dilatation. Another feature is the presence of transependymal adsorption (Figure 4) evaluated as a low density on CT scan or a high intensity on T2WI MRI. Again, the evaluation of the degree of compression on the sulci of the convexity, which could help to differentiate iNPH from the various forms of dementia, associated with a dilated sylvian fissure (Figure 5) [17–20]. The changes in subarachnoid spaces are evident even in cingulate gyrus as cingulate sulcus sign (Figure 6): posterior half of cingulate sulcus is narrower than the anterior half [21,22]. Another feature is the widening of the frontal corridors and the rounding of the third ventricle, in the coronal plane. In general, the conspicuous dilatation of the ventricular system causes a thinning of the corpus callosum pushing it upwards, this protrusion is limited at the top by the great falx, which is why the corpus callosum impinges along the midline and is pushed laterally by the lateral ventricles decreasing the angle it normally forms: this parameter is called acute callosal angle (<90°), measurement that should be carried out, on coronal plane, at the level of the posterior commissure (Figure 7) [19]. The enlargement of ventricular system causes a widening of the temporal horns of the lateral ventricles >2mm (Figure 8). However, in clinical practice, these features are little evaluated; usually refers to the Evans index. It is defined as the ratio of largest width of the frontal horns to maximal biparietal diameter (of the brain and not of the bone) at the same CT slice (Figure 10). Cut-off is 0.3. >0.3 suggest hydrocephalus. Asymptomatic ventriculomegaly with features iNPH on MRI (AVIM) is a finding of disproportionately enlarged subarachnoid space hydrocephalus without neurologic symptoms. Some authors believe that AVIM is a pre-clinical form of iNPH [23].

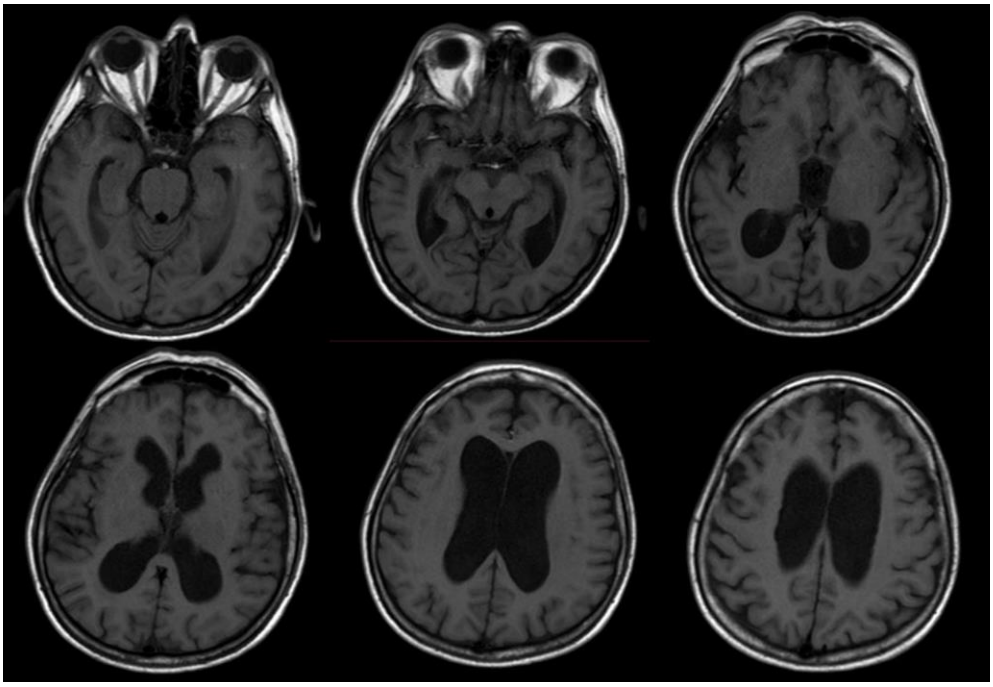

Figure 1. MRI allows to evaluate degree and location of the dilatation of the ventricular system.

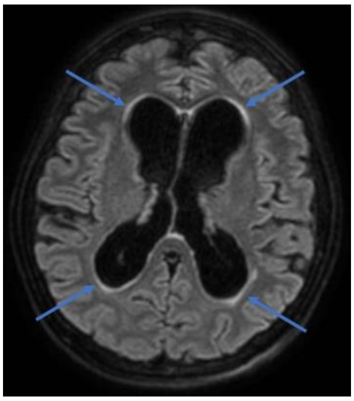

Figure 2. Blue arrows showing transependymal absorption in axial MR view.

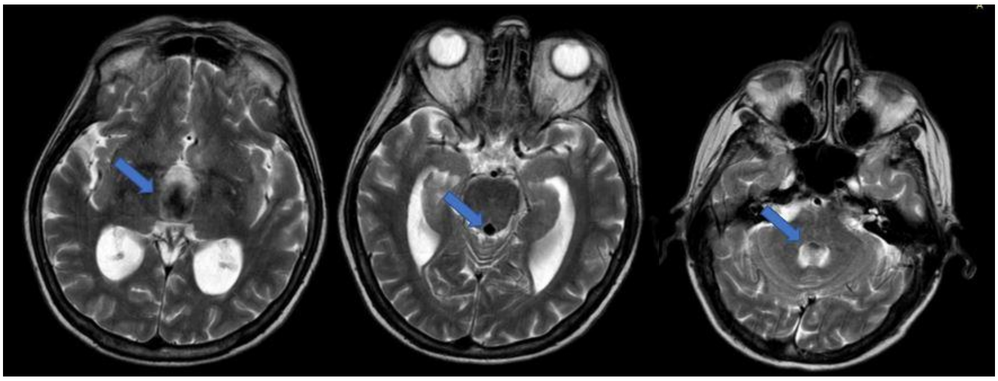

Figure 3. Blue arrows indicating CSF tourbolences in third and fourth ventricles and acqueduct.

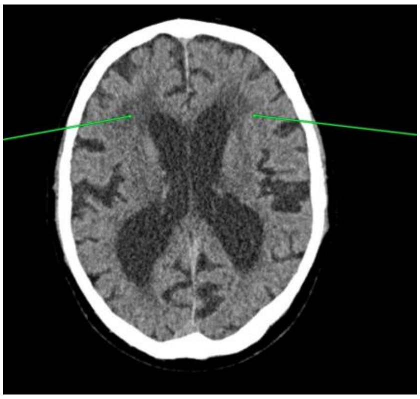

Figure 4. Green arrows showing transependymal absorption in axial CT view.

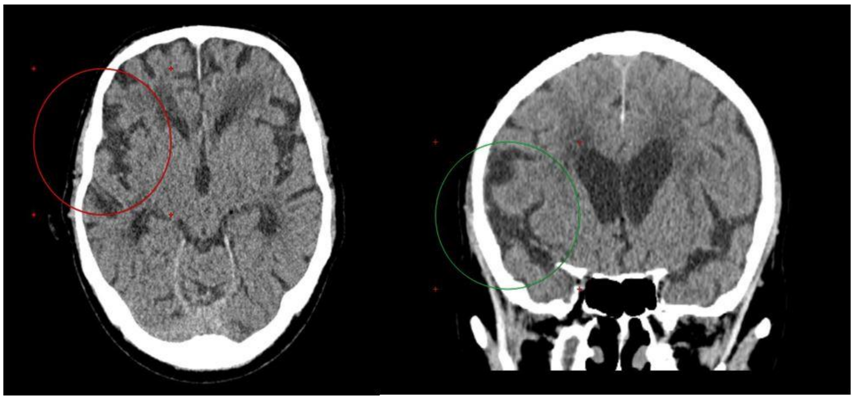

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Figure 5. CT scan shows dilated sylvian fissure in axial and coronal sequences, from left to right respectively.

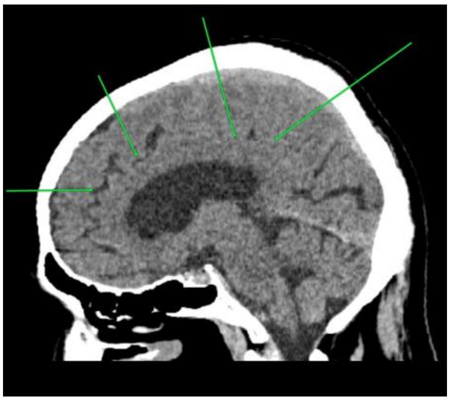

Figure 6. Green arrows show half of cingulate sulcus narrower than the anterior half in a sagittal CT scan.

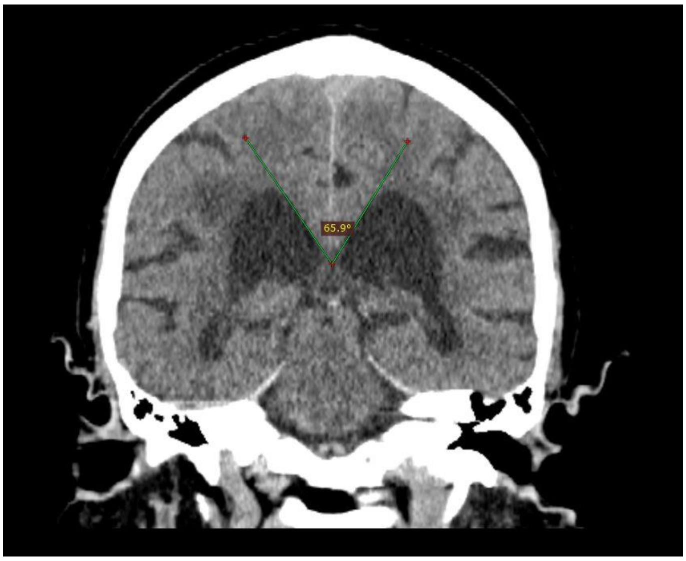

Figure 7. Callosal angle, on coronal plane, measured at the level of the posterior commissure. Acute callosal angle is a parameter of hydrocephalus.

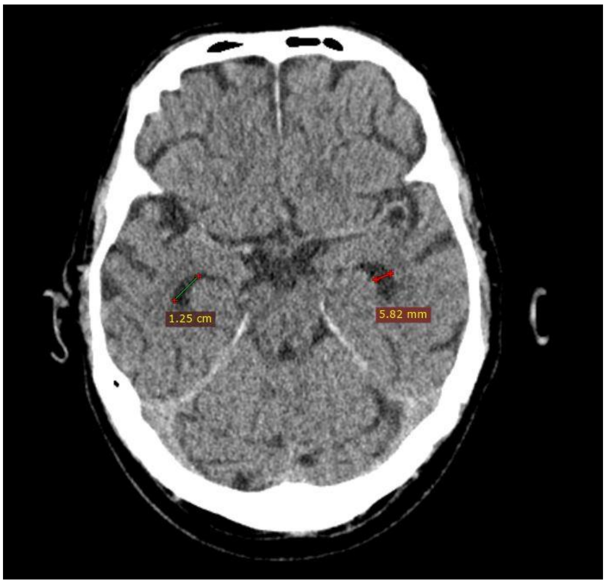

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Figure 8. Widening of the temporal horns of the lateral ventricles.

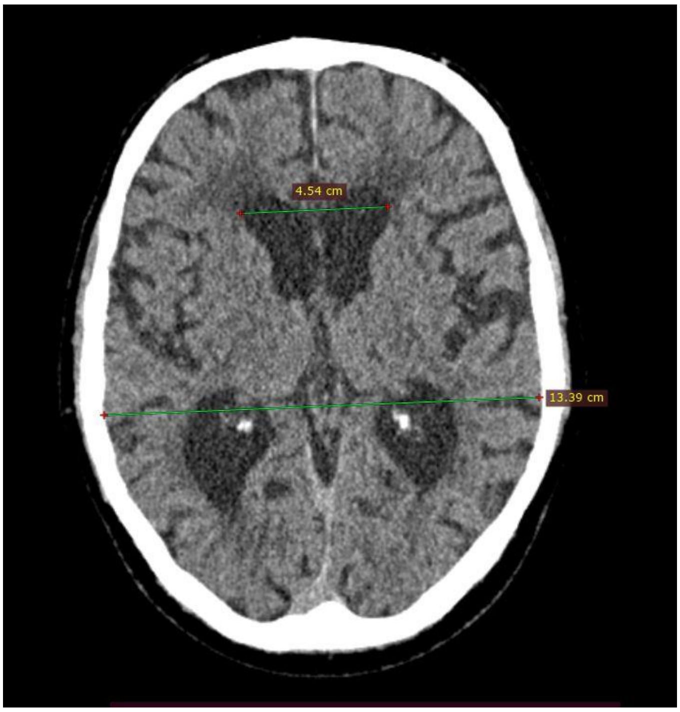

Figure 9. Evans' index (4,54 / 13,39 = 0,34).

Neuropsychological Assessment

Neuropsychological assessment may help in differential diagnosis. Indeed, compared to other forms of dementia, iNPH is characterized by a dysfunction of executive functions and short-term memory at the cognitive level [24],[25]. Conversely, AD is characterized by a global cognitive dysfunction that affects all cognitive functioning rather than individual specific functions. In this study, we investigated the role of qualitative analysis of systematic errors in the early detection of patients with iNPH. According to our previous study [26], qualitative analysis of percentage of errors in neuropsychological evaluation is more sensitive than quantitative evaluation in identifying patients with suspected iNPH. Studies in the literature assume the post ELD improvement as the only discriminating factor between iNPH and non-iNPH patients [27]. ELD is a valid tool to recognize patients who will benefit from shunting since the positive test response is very reliable. Contrarily, negative tests response is not so reliably to decide ineligibility for shunting [28]. Our patients were divided into two groups (iNPH and non-iNPH) based on the type of cognitive dysfunction, post-procedure improvement, and the presence of iNPH and non-iNPH neuropsychological patterns during the neuropsychological assessment performed before and after ELD. The iNPH patients did not have a severe dysfunction of global cognitive functioning, confirming the hypothesis that iNPH is related with a decline in frontal functioning. Furthermore, when compared to non-iNPH patients, the group of iNPH patients demonstrated a dissociation between the performance of phonological fluency tasks and semantic fluency tasks. Phonological fluency activates the posterior part of the left inferior frontal cortex and the left premotor area more than semantic fluency. This data would confirm the frontal damage of iNPH patients. In iNPH, phonological fluency is a severely compromised executive function. Short-term memory is also a cognitive ability that is impaired in iNPH.

Our case series had severe impairments, but only the iNPH patients improved after ELD. However, these data, like those on executive functioning and global cognitive functioning, lacks in predictability. They fail to differentiate between iNPH and non-iNPH patients at time zero (T0), offering only a distinction based on the severity of symptoms presented. As a result, we proposed a qualitative analysis of systematic errors. At T0, we distinguish two types of responses between the iNPH and non-iNPH groups in order to predict the utility of ELD. In 1935, Mayer Gross described the closing-in phenomenon (tendency to close on a model during the execution of a praxico-constructive task) as a typical neuropsychological pattern of patients with AD. This phenomenon was later identified as a highly sensitive and specific pattern of the AD in subsequent studies [29],[30]. In our study, all patients who presented this phenomenon were included in non-iNPH group and did not improve after ELD, demonstrating the predictive value of this type of response. The type of error in the response to PM47 revealed a further neuropsychological pattern with predictive value. In our study, patients who did not improve after ELD had a significant frequency of incorrect global responses. Conversely, patients who improved significantly after ELD had a significant frequency of providing erroneous responses for stimulus orientation. Therefore, these features guided us distinguish between iNPH patients who will potentially benefit from shunting and non-iNPH patients. The neuropsychological patterns identified have a high specificity for distinguishing iNPH from non-iNPH symptomatology. The analysis of these phenomena could be used at the time zero assessment for an early differential diagnosis, being also able to predict the potential usefulness of a ELD test. Our findings highlight the importance of a comprehensive neuropsychological evaluation in the diagnosis of this ambiguous pathology, as well as the significant value of qualitative analysis in terms of predictability. This protocol could thus be a helpful tool in the early screening of elderly patients with suspected iNPH in order to determine who should undergo an invasive procedure such as the EDL.

5. Conclusions

Our study was subject to limitations, including a modest sample size, not differentiation among the presence of other pathologies (e.g., diabetes, hypertension, etc...), symptoms onset and severity, and presence of mood disorders. This may be a limitation given the potential influence of these factors on cognitive test data and result in a reduction in statistical power that limited the range of potential analyses.

Although our protocol has had wide inclusion criteria, the result confirms that iNPH symptoms can be confused with those of other neurodegenerative diseases for which a standardized protocol is needed. Our protocol aim is to identify patients who will benefit from surgery through ELD test. Neuropsychological assessment offers a useful additional tool for differential diagnosis. We found significant improvements in neuropsychological test results after ELD in 28 of the 44 patients. There were no quantitative tests able to predict these changes and to provide differential diagnosis during the initial evaluation. Only the qualitative analysis of the systematic errors found a new reading key, predicting the post ELD result. If systematically applied and interpreted, qualitative analysis of systematic errors can invaluably contribute to the diagnosis and management of iNPH, managing to have predictive value in the post ELD assessments.

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