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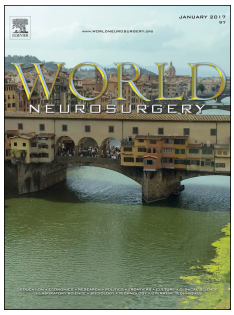

Global Neurocognitive and Frontal Functions analysis and Precision Intrathecal Pressure Measurement to Settle the Diagnostic Dilemma of the Normal Pressure Hydrocephalus: a preliminary experience.

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Global Neurocognitive and Frontal Functions analysis and Precision Intrathecal Pressure Measurement to Settle the Diagnostic Dilemma of the Normal Pressure Hydrocephalus: a preliminary experience.

Short Title: *Neuropsychology and Lumbar infusion Test in NPH diagnosis*

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Keywords*: Normal Pressure Hydrocephalus, Lumbar Infusion, Tap Test, MRI, Neuropsychology.*

Introduction: Normal Pressure Hydrocephalus (NPH) is a common condition associated with a cognitive deterioration and possibly involving up to 9-14% of all the over 65 years old nursing home residents. The purpose of the present paper is to introduce an inclusive study protocol aimed at increasing the diagnostic precision and follow-up accuracy.

Methods: A total of 28 patients were operated on for NPH in our institution in the period ranging between January 2015 and December 2019. All the patients underwent a brain MRI scan with standard sequences, calculation of the Evans Index and Corpus Callosum Angle, evaluations by means of MOCA, MMSE and FAB neuropsychological tests preoperatively, at 1 and 6 months. A preoperative lumbar test infusion(LIT) with fine measurement of the intrathecal pressures at the beginning and at the end of the procedures was performed.

Results: MOCA and FAB proved an overall improvement of the neurocognitive conditions at 1 month postoperatively. The mean pressure at the beginning of the LIT, was negatively associated to the neuropsychological outcome variables (MMSE, FAB and MOCA) in the three different evaluations, with FAB and MOCA at 6 months. We found a strong positive correlation between the Evans Index as measured on the first MRI scan both with the diastolic and systolic pressure at the beginning of the test.

Conclusions: Neuropsychological assessment, combined with LIT with intrathecal pressure managements aids the diagnostic process in patients affected by NPH. It allows standardizing in a rigorous fashion the follow-up evaluation of patients undergoing surgery for VPS.

Global Neurocognitive and Frontal Functions analysiscombined with Precision Intrathecal Pressure Measurement to settle the diagnostic Dilemma of the Normal Pressure Hydrocephalus: Preliminary experience.

Short Title: *Neuropsychology and Lumbar infusion Test in NPH diagnosis*

Introduction

Recent studies outline that approximately as high as 50 million individuals are affected by dementia worldwide. Nearly 10% of all patients suffering from cognitive deterioration symptoms are affected by Normal Pressure Hydrocephalus (NPH)[1,2]. This condition involves especially the elderly, over 65 years. It could be the correct diagnosis in up to 9-14% of all the over 65 years old nursing home residents[3-5]. being often misdiagnosed with different clinical dementia related conditions[1]. Many radiological parameters have been investigated as connected with the diagnosis of NPH, such as the corpus callosum angle (CCA), Evan's Index (EI), the presence of transventricular reabsorption sings (FE), and the dimension of the ventricles. Also, clinical parameters, and indexes of cognitive performance, such as Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA)[6,7]. are frequently accounted for. All this multidimensional picture should be studied to achieve what is allegedly the most critical target in NPH surgery: an unquestionable diagnosis. The Lumbar Infusion Test (LIT), and the Lumbar Tap Test (LTT) based on an invasive intrathecal "infusion" and intrathecal pressure measurement stands as a completely separate chapter in the diagnosis of NPH, being reported to increase the diagnostic accuracy of NPH in some series[8], while substantially inaccurate in others[9]. What the LIT offers is a direct barometric measurement of the intrathecal pressure, along with precise pressure values whose correlations with the neuropsychological and radiological parameters have yet to be explored andunderstood.

The aim of this retrospective study was to analyze the long-term results, the prognostic impact of many radiological and clinical parameters, in patients operated on using a ventriculo-peritoneal shunt

(VPS). Primary targetwas to shed light over their ultimate and widely unexplored relationship with the intrathecal pressure measurements.

Materials and Methods

Study design and Setting

In the period between January 2015 and December 2019, a total of 37 patients underwent VPS implantation for the management of a NPH in our institution. The design of the study is a retrospective observational cohort analysisin which the data were collected by two researchers (A.S. and G.P.), who were blinded to the objective and design of the study.

Participants and Eligibility

The enrollment in the study was performed according to the following criteria:

1. Patients who underwent a preoperative LIT, whose results were coherent with a NPH diagnosis (in particular anElastance value ≥ 0.3 [1/ml]),
2. Availability of all the values of pressure of the preoperative LIT,
3. Patients who received at least a two-step follow-up at 1 and 6 months, with clinical and neuropsychological reevaluations.
4. Patients underwent a superimposable radiological protocol, at the same moment of the clinical reevaluations.
5. Patients who experienced a major postoperative complication such as intracranial bleeding, intracranial or abdominal infection, or shunt misplacement or malfunction, practically whose intraventricular pressure could not be relieved as an effect of the shunt positioning were excluded from the study.

6. Patients whose clinical or surgical data were incomplete, missing, or incorrect were *a priori* excluded from the final cohort.
7. We excluded all the patients who had previous history of condition possibly influencing the development of a hydrocephalus, namely, subarachnoid hemorrhage, traumatic brain injury and intracranial infections, intracranial tumors and ventricular congenital malformations.

Lumbar Infusion Test was performed according to a protocol, previously reported[10] and we considered the test reliable if R2, the coefficient of determination, is > 0.8

Radiological Protocol

All the patients meeting inclusion criteria underwent a preoperative brain MRI scan (Fig 1) included in high field 1.5 Tesla volumetric study with the following sequences: T1w, T2w, FLAIR, isotropic volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) anddiffusion tensor sequences (DTI). MRI was repeated, with the same sequences, at 1 and 6 months of follow-up, when reevaluating the patients from a clinical and neuropsychological perspective and when repeating the LIT. In all cases, on the ground of the MRI imaging the Evans Index (EI) and the Corpus Callosum Angle (CCA) were calculated, as reported elsewhere[7,20.] Moreover, the dimension of the ventricles was recorded, as a continuous variable in cm, on the ground of their Evans measurements, and the presence of transependymal reabsorption radiological signs as well as the enfacement of the parietal gyri were recorded as dichotomous variables (0/1 – No/Yes).All the patients underwent in any case an early control by means of a brain CT scan and an abdominal plain X-ray film to confirm, respectively, the proper positioning of the intracranial and peritoneal end of the shunting system.

Clinical and Neuropsychological evaluation

All the patients were investigated from a neuropsychological and cognitive performance perspective. Among the different psychometric instruments, with the aid of a neuropsychologist, we selected a dedicated battery composed of Mini Mental Status Examination (MMSE), Montreal Cognitive Assessment (MOCA) and Frontal Assessment Battery (FAB), as descriptive of a global cognitive functioning. The psychometric, sensitivity and specificity issues are discussed elsewhere[6,11-13]. A subjective anamnestic report of improvement/not improvement of the preoperative urinary incontinence symptoms was considered. The cognitive function as well as the mobility and urinary symptoms were evaluated preoperatively, at 1 and 6 months. The results of the last two parameters was codified in a three-step ordinal variable as follows: 0/1/2 – "Worsened"/"Stable"/"Improved at least one".

Surgical Protocol, device and pressure selection

All the patients were operated on with a standard total intravenous anesthesia protocol, in a standard VPS fashion. In all cases the implanted valve was an adjustable MiethkeproGAV 2.0 (B-Braun, Tuttlingen, Germany), with a soft reservoir for tactile feedback. The initial pressure was set on 140 mmH20, and then possibly adjusted on the ground of the radiological and clinical findings. The 140 mmH20 initial value is, according to our opinion, an optimal value for further up- and down-scaling, in case of need, considering that the appropriate value for each patient can vary also significantly over time.

Statistical methods

The sample was analyzed with SPSS version 18. Comparison between nominal variables have been made with Chi^2 test. Means of continuous variables, as investigated per ordinal, nominal of dichotomous variables were compared with One Way and Multivariate ANOVA analysis along with

Contrast analysis and Post-Hoc Tests. Continuous variables correlations have been investigated with Pearson's Bivariate correlation. Threshold of statistical significance was considered $p<.05$.R^2 analysis was used to evaluate the reliability of each test.

We addressed no missing data since incomplete records were an exclusion criteria.

Ethics

The study was approved by the Institutional Review Board. Before surgical procedure, all the patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed. This study is consistent with Helsinki declaration of Human Rights.

Results

A total of 28 patients were selected according to the aforementioned inclusion and exclusion criteria, 11 males and 17 females whose average age at the time of the diagnosis was 74.14±4.96.The average R_{out}, Intracranial Elastance, R^2 (coefficient of determination of the Intracranial Elastance) and Diastolic/Systolic pressure at the beginning and at the end of the LIT are reported in detail in Table 1. The values of means of pressure parameters at the beginning and at the end of the LIT, showed, as expected, a statistically significant difference ($p= 0.0001$).

Considering the dimension of the cohort and the rigorousness of the experimental protocol, and consistently with our previous evidence of better outcomes associated to an Elastancevalue of ≥ 0.3, all the included patients suggestedsubjective improvement of their clinical conditions. The Paired Samples T-Tests confirmed, from a neuropsychological perspective this impression (Fig 2), beyond the threshold of statistical significance for both MOCA and FAB. Interestingly MMSE, which was included in the protocol as descriptive of the neurocognitive functioning, reported to be a simple and reliable instrument for other conditions implying a global cognitive decline such as Alzheimer and

Neurovascular Dementia, failed to reach the threshold of statistical significance (p between 0.140 and 0.193).

All of the patients enrolled had a LIT proven Elastancevalue over 0.3 (Mean 0.63 1/mL, Range 0.3-1.3 CI95% 0.54-072), whereas R_{out} parameters were on average16.8±10.20 (CI 95% 14.29-21.47). Interestingly, Elastance did not show an association as predictor of better neuropsychological outcomes, while notably, R_{out} was also positively associated to the dimension of the ventricles after shunting (r=.682 with p=.021), and negatively associated to the total variation of the dimension of the ventricles between the pre- and post-shunting MRI scans (r=-.552 with p=.123).

All the investigated "end" and "beginning" LIT pressure values (diastolic, systolic, mean) had statistical associations between each other (r between .354 and .993 with p between 038. and .001). However,the mean pressure demonstrated a trend towards a negative associationwith the neuropsychological outcome variables (MMSE, FAB and MOCA). For FAB and MOCA at 6 months, this association reached the statistical significance in the case of FAB (respectively r =-.849 and r =-.550 with p=.008 and p=.150). Diastolic and systolic pressure failed to reach the statistical significance in predicting the neurocognitive performance scores. Nevertheless, they demonstrated interesting correlations with the radiological findings. We found a strong positive correlation between the Evans Index as measured on the first MRI scan both with the diastolic and systolic pressure at the beginning of the test (r respectively r=.615 and .620 both p=.001 – Fig 3). The same association was present at the end of the LIT, with no statistical significance (respectively r=.286 and .235 with p=.136 and p=.094). This finding confirmsEI as predictor of a correct NPH diagnosis, demonstrating a direct association between the intraventricular pressure and the EI itself.

Univariate and Repeated measures ANOVA analyses completed the test panel. Univariate ANOVA analysis showed an interesting strong statistical correlation between the absence of Flow Void signal in the preoperative and follow up MRI and the ventricular dimension.It possibly highlights the multifactorial pathogenesis of the NPH, notonly a functional reduction of the CSF outflow but a

concurrent structural problem of the ventricular walls and their Elastance (p=.013 – Fig 4). Moreover,it showsa univariate trend towards association between the visualization of the lower CCA and the visualization of the sylvian fissure (p=.058).

A Repeated measure ANOVA analysis outlined a role of the presence/absence of the Flow Void signal and the sylvian fissure visualization and the better neuropsychological scores (Fig 5). In particular, it reached the statistical significance for what MOCA scores, over the follow-up period are concerned (p=.004) whereas it was a non-significant trend in respect to the FAB and MMSE (respectively p=.076 and .094).

According to previously mentioned reasons we regarded the complications as an exclusion criteria. A total of two patients were excluded from the present cohort because of surgical complications, both requiring a second surgery. The first patient experienced a VPS infection, and underwent a second surgery to remove the entire implant. The second patient underwent a second surgery of a hemispheric craniectomy for the management of an acute subdural hematoma.

Discussion

Infusion test represents the gold standard exam to predict the outcome in patients affected by NPH[14]. It can be performed in two anatomic areas: directly inside the ventricular system or through the lumbar subarachnoid space. There are several differences between the two techniques, such as: ventricular procedure is more invasive and must be carried out in the operating room; on the other hand, the registration is more accurate and, if the test turns out positive, it is possible to perform immediately the VPS by using the same ventricular entry point chosen for the exam[15]. In both procedures basal pressure is registered for around 10 minutes at steady state, then the infusion of saline solution is performed at 1 ml per minute for about 30 minutes. The test can be interrupted if the patient refers

intracranial hypertension symptoms such as headache or nausea, or if pressure values exceed 40 mmHg. LIT, similarly to the ventricular infusion test, allows to register different parameters related to CSF circulation and pressure, such as: mean, systolic, diastolic and pulsatile ICP before, during and after the infusion of saline solution; ICP pulse wave morphology during and after the procedure; R_{out} and elasticity[16,17]. It should be regarded as less a less invasive test method in respect to its ventricular counterpart. Among those pressure measurements, Elasticity should be considered the most determinant factor in predicting surgical outcome in NPH patients: values higher than 0.3 might represent a strong positive predicting element of shunting favorable outcome[16].

Regarding the role of R_{out} in predicting surgical outcome of VPS, it has been described in several studies that for values ranging from 12 to 18 mmHg, R_{out} is not that much reliable parameter[16,18]. Conversely, values of R_{out} lower than 12 mmHg are associated with an higher probability of lack of clinical improvement after VP shunting, while for values higher than 18 mmHg it has been shown the good probability of favorable surgical outcome[19,20]. However, the results retrieved from our data analysis highlight that patient with higher values of R_{out} showed poorer neuropsychological outcome at follow-up. Moreover, it is noteworthy the positive correlation between high values of R_{out} and the dimension of the ventricles after shunting and the negative one with the total variation of the dimension of the ventricles between the pre- and post-shunting MRI scans. In fact, these data suggest that the ventricular walls of the patients presenting higher R_{out} had a lesser tendency to reduce their diameter after the positioning of the VPS, which might be confirmed by radiological findings. In the specific case of R_{out}, the message derived from our experience is that it should not be regarded as an unquestionably reliable parameter neither concerning the diagnosis nor the prognosis of NPH patients.

Several studies outlined the correlation between reduction of EI and outcome. More specifically, it has been described that EI usually does not change in unimproved patients, while in the 40% of improved patients, EI decreases1[6]. Therefore, decrease of ventricular diameter is not associated

necessarily to favorable outcome [21,22]. There are two main hypothesis that could explain the non-linear association between EI decrease and outcome: discrepancy between current shunting devices efficiency and pathological mechanisms that cause hydrocephalus; irreversible structural changes in brain parenchyma that not do correlate with neurological recovery after shunting. However, on the base of the association between EI and values of diastolic and systolic pressure outlined in the Results section, it could be interesting to explore how structural changes affect not only post-operative decrease of ventricular diameters, but ICP as well.

In normal subjects the radiological phenomenon of flow void is usually located in the sylvian aqueduct. However, it is well-known that in patients affected by NPH, the flow void signal is extended through the third and the fourth ventricles, often with the coexisting presence of CSF reflux[23,24]. These particular findings outline that in NPH ventricular circulation is hyperdynamic and it has been reported that greater extension of the CSF flow void could most likely be related to increased ventricular volumes[25]. Therefore, the presence of flow void has been studied as a possible predicting factor for VPS surgical outcome, without reaching satisfying results[25]. More specifically, the most relevant pitfall is represented by the fact that the absence of flow void signal cannot exclude the presence of NPH[26]. In fact, as stated before, the present study outlines those bigger ventricular volumes and worse neuropsychological outcome have been detected in patients without CSF flow void at pre- and post-operative MRI, confirming this feature regarding the radiological study of ventricular circulation in NHP.

Limitations

The preoperative and postoperative study protocol was rigorous and is extremely homogeneous for all the patients included nevertheless, several limitations need to be considered in the experimental design. First, the retrospective nature of the study. In addition, we mention the variability in the final positioning of the valve, minimal parenchymal bleeding or adhesion phenomena which could cause occlusion of a part of the holes of the proximal shunt, resulting in different shunting volumes, or

abdominal *noxae* partially and subclinical impairing the distal shunt, which could have jeopardized the results. Although a major effort was paid in homogeneously studying and following up the patients, and although the presented protocol appears to be promising, some of the reported results could suffer from the relative exiguity of the statistical sample.

Conclusions

A fine neuropsychological assessment, combined with LIT significantly aids the diagnostic process in patients affected by NPH. Moreover, such an approach can possibly standardize in an extremely rigorous fashion the follow-up evaluation of patients undergoing surgery for VPS. Elastance values ≥ 0.3 (1/ml), are associated with better functional and clinical outcomes, and could be regarded as key values to elect a patient to a VPS surgery.

References:

1. Reeves BC, Karimy JK, Kundishora AJ, Mestre H, Cerci HM, Matouk C, Alper SL, Lundgaard I, Nedergaard M, Kahle KT. Glymphatic System Impairment in Alzheimer's Disease and Idiopathic Normal Pressure Hydrocephalus. *Trends Mol Med*. 2020 Mar;26(3):285-295. doi: 10.1016/j.molmed.2019.11.008. Epub 2020 Jan 18. PMID: 31959516; PMCID: PMC7489754.
2. Nassar BR, Lippa CF. Idiopathic Normal Pressure Hydrocephalus: A Review for General Practitioners. *GerontolGeriatr Med*. 2016 Apr 20;2:2333721416643702. doi: 10.1177/2333721416643702. PMID: 28138494; PMCID: PMC5119812.
3. Kiefer M, Unterberg A. The differential diagnosis and treatment of normal-pressure hydrocephalus. *DtschArztebl Int*. 2012 Jan;109(1-2):15-25; quiz 26. doi: 10.3238/arztebl.2012.0015. Epub 2012 Jan 9. PMID: 22282714; PMCID: PMC3265984.

4. Wallenstein MB, McKhann GM 2nd. Salomón Hakim and the discovery of normal-pressure hydrocephalus. *Neurosurgery*. 2010 Jul;67(1):155-9; discussion 159. doi: 10.1227/01.neu.0000370058.12120.0e. PMID: 20568668.
5. Martín-Láez R, Caballero-Arzapalo H, Valle-San Román N, López-Menéndez LÁ, Arango-Lasprilla JC, Vázquez-Barquero A. Incidence of IdiopathicNormal-Pressure Hydrocephalusin Northern Spain. *World Neurosurg*. 2016 Mar;87:298-310. doi: 10.1016/j.wneu.2015.10.069. Epub 2015 Nov 5. PMID: 26548835.
6. Matsuoka T, Kawano S, Fujimoto K, Kawahara M, Hashimoto H. Characteristics of cognitive function evaluation using the Montreal cognitive assessment in a cerebrospinal fluid tap test in patients with idiopathic normal pressure hydrocephalus. *Clin Neurol Neurosurg*. 2019 Nov;186:105524. doi: 10.1016/j.clineuro.2019.105524. Epub 2019 Sep 12. PMID: 31541862.
7. Griffa A, Bommarito G, Assal F, Herrmann FR, Van De Ville D, Allali G. Dynamic functional networks in idiopathic normal pressure hydrocephalus: Alterations and reversibility by CSF tap test. *Hum Brain Mapp*. 2020 Dec 9. doi: 10.1002/hbm.25308. Epub ahead of print. PMID: 33296129.
8. Kahlon B, Sundbärg G, Rehncrona S. Comparison between the lumbar infusion and CSF tap tests to predict outcome after shunt surgery in suspected normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry*. 2002 Dec;73(6):721-6. doi: 10.1136/jnnp.73.6.721. PMID: 12438477; PMCID: PMC1757331.
9. Savolainen S, Hurskainen H, Paljärvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. *Acta Neurochir (Wien).* 2002 Jun;144(6):515-23; discussion 523. doi: 10.1007/s00701-002-0936-3. PMID: 12111484.
10. Hashimoto M, Ishikawa M, Mori E, Kuwana N; Study of INPH on neurological improvement (SINPHONI). Diagnosis of idiopathic normal pressure hydrocephalus is

supported by MRI-based scheme: a prospective cohort study. *CerebrospinalFluid Res*. 2010 Oct31;7:18. doi: 10.1186/1743-8454-7-18. PMID: 21040519; PMCID: PMC2987762.

11. Matsuoka T, Akakabe M, Iida JI, Kawahara M, Uchiyama Y. Changes in Cognitive Function Scores After Cerebrospinal Fluid Tap Testing in Patients with Suspected Idiopathic Normal-Pressure Hydrocephalus. *CognBehavNeurol*. 2018 Dec;31(4):201-206. doi: 10.1097/WNN.0000000000000176. PMID: 30562229.
12. Ko PW, Lee HW, Kang K. Frontal Assessment Battery and Cerebrospinal Fluid Tap Test in Idiopathic Normal-Pressure Hydrocephalus. *Eur Neurol*. 2017;77(5-6):327-332. doi: 10.1159/000472712. Epub 2017 May 5. PMID: 28472801.
13. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991 Feb;39(2):142-8. doi: 10.1111/j.1532-5415.1991.tb01616.x. PMID: 1991946.
14. Petrella G, Czosnyka M, Smielewski P, Allin D, Guazzo EP, Pickard JD, Czosnyka ZH. In vivo assessment of hydrocephalus shunt. *Acta Neurol Scand*. 2009 Nov;120(5):317-23. doi: 10.1111/j.1600-0404.2009.01176.x.Epub 2009 May 20. PMID: 19456302.
15. Eide PK, Brean A. Intracranial pulse pressure amplitude levels determined during preoperative assessment of subjects with possible idiopathic normal pressure hydrocephalus. *Acta Neurochir (Wien).* 2006 Nov;148(11):1151-6; discussion 1156. doi: 10.1007/s00701-006-0896-0. Epub 2006 Oct 16. PMID: 17039303.
16. Anile C, De Bonis P, Albanese A et al. Selection of patients with idiopathic normal-pressure hydrocephalus for shunt placement: a single institution experience. *J Neurosurg* 2010; 113:64-73.
17. Skalický P, Mládek A, Vlasák A, De Lacy P, Beneš V, Bradáč O. Normal pressure hydrocephalus-an overview of pathophysiological mechanisms and diagnostic procedures. *Neurosurg Rev*. 2020 Dec;43(6):1451-1464. doi: 10.1007/s10143-019-01201-5. Epub 2019 Nov 8. PMID: 31705404.

18. Boon AJ, Tans JT, Delwel EJ et al. Dutch normal pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *J Neurosurg* 1997; 87:687-93.

19. Dehvel EJ, de Jong DA, Avczaac CJ. The prognostic value of clinical characteristics and parameters of cerebrospinal fluid hydrodynamics in shuncing for idiopathic normal pressure hydrocephalus. *Acta Neurochir (Wien)* 2005; 147:1037-42

20. Malm J, Jacobsson J, Birgander R et al.al. Reference values for CSF outflow resistance and intracranial pressure in healthy elderly. *Neurology* 2011; 76:903-9.

21. Meier U, Mutze S: Correlation between decreased ventricular size and positive clinical outcome following shunt placement in patients with normal-pressure hydrocephalus. *J Neurosurg*100:1036–1040, 2004

22. Meier U, Paris S, Gräwe A, Stockheim D, Hajdukova A, Mutze S: Is there a correlation between operative results and change in ventricular volume after shunt placement? A study of 60 cases of idiopathic normal-pressure hydrocephalus. *Neuroradiology* 45:377–380, 200

23. Bradley WG Jr. Idiopathic normal pressure hydrocephalus: new findings and thoughts on etiology. *Am J Neuroradiol* 2008; 29:1-3. 133

24. Scollato A, Gallina P, Gautam B et al. Changes in aqueductal CSF stroke volume in shunted patients with idiopathic normal-pressure hydrocephalus. *Am J Neuroradiol* 2009; 30:1580-6.

25. Krauss JK, Regel JP, Vach W, Jüngling FD, Droste DW, Wakhloo AK. Flow void of cerebrospinal fluid in idiopathic normal pressure hydrocephalus of the elderly: can it predict outcome after shunting? *Neurosurgery.* 1997 Jan;40(1):67-73; discussion 73-4. doi: 10.1097/00006123-199701000-00015. PMID: 8971826.

26. Hurley RA, Bradley WG Jr, Latifi HT, Taber KH. Normal pressure hydrocephalus: significance of MRI in a potentially treatable dementia. *J NeuropsychiatryClinNeurosci.* 1999 Summer;11(3):297-300. doi: 10.1176/jnp.11.3.297. PMID: 10440004.

Figure and Table legends

Table 1 – Descriptive statistics of measured variables

Figure 1 – An MRI scan demonstrating the typical NPH. A. Evans index, B. Corpus Callosum Angle

Figure 2 –Paired samples T Tests demonstrating the neuropsychological scores of A. MMSE, B. FAB and C. MOCA over the 6 months of follow-up. In B (FAB) and C (MOCA) it is possible to appreciate a statistically significant improvement when comparing the preoperative and 6 months follow-up evaluations.

Figure 3 – Pearson's bivariate correlation demonstrating the systolic and diastolic average pressures and their correlation with the Evans Index

Figure 4 – Univariate ANOVA analysis demonstrating the relationship between the presence of Flow Void and the Ventricular Diameters. The absence of the flow void sign is associated to a greater ventricular size.

Figure 5 – Repeated Measures ANOVA analysis demonstrating the role of the presence absence of Flow Void and Sylvian Fissure signs' in respect to the neuropsychological outcome variables in particular in A and B with FAB, in C and D with MOCA and in D and E with MMSE. There was a statistical significant favorable progression of the MOCA scores, over the follow-up period (p=.004), while there was a non-significant trend in respect to the FAB and MMSE (respectively p=.076 and .094).

Colors should be used in any figure in print

27. Reeves BC, Karimy JK, Kundishora AJ, Mestre H, Cerci HM, Matouk C, Alper SL, Lundgaard I, Nedergaard M, Kahle KT. Glymphatic System Impairment in Alzheimer's

Disease and Idiopathic Normal Pressure Hydrocephalus. Trends Mol Med. 2020 Mar;26(3):285-295. doi: 10.1016/j.molmed.2019.11.008. Epub 2020 Jan 18. PMID: 31959516; PMCID: PMC7489754.

28. Nassar BR, Lippa CF. Idiopathic Normal Pressure Hydrocephalus: A Review for General Practitioners. GerontolGeriatr Med. 2016 Apr 20;2:2333721416643702. doi: 10.1177/2333721416643702. PMID: 28138494; PMCID: PMC5119812.
29. Kiefer M, Unterberg A. The differential diagnosis and treatment of normal-pressure hydrocephalus. DtschArztebl Int. 2012 Jan;109(1-2):15-25; quiz 26. doi: 10.3238/arztebl.2012.0015. Epub 2012 Jan 9. PMID: 22282714; PMCID: PMC3265984.
30. Wallenstein MB, McKhann GM 2nd. Salomón Hakim and the discovery of normal-pressure hydrocephalus. Neurosurgery. 2010 Jul;67(1):155-9; discussion 159. doi: 10.1227/01.neu.0000370058.12120.0e. PMID: 20568668.
31. Martín-Láez R, Caballero-Arzapalo H, Valle-San Román N, López-Menéndez LÁ, Arango-Lasprilla JC, Vázquez-Barquero A. Incidence of IdiopathicNormal-Pressure Hydrocephalus in Northern Spain. World Neurosurg. 2016 Mar;87:298-310. doi: 10.1016/j.wneu.2015.10.069. Epub 2015 Nov 5. PMID: 26548835.
32. Matsuoka T, Kawano S, Fujimoto K, Kawahara M, Hashimoto H. Characteristics of cognitive function evaluation using the Montreal cognitive assessment in a cerebrospinal fluid tap test in patients with idiopathic normal pressure hydrocephalus. Clin Neurol Neurosurg. 2019 Nov;186:105524. doi: 10.1016/j.clineuro.2019.105524. Epub 2019 Sep 12. PMID: 31541862.
33. Griffa A, Bommarito G, Assal F, Herrmann FR, Van De Ville D, Allali G. Dynamic functional networks in idiopathic normal pressure hydrocephalus: Alterations and reversibility by CSF tap test. Hum Brain Mapp. 2020 Dec 9. doi: 10.1002/hbm.25308. Epub ahead of print. PMID: 33296129.
34. Kahlon B, Sundbärg G, Rehncrona S. Comparison between the lumbar infusion and CSF tap tests to predict outcome after shunt surgery in suspected normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 2002 Dec;73(6):721-6. doi: 10.1136/jnnp.73.6.721. PMID: 12438477; PMCID: PMC1757331.
35. Savolainen S, Hurskainen H, Paljärvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. Acta Neurochir (Wien). 2002 Jun;144(6):515-23; discussion 523. doi: 10.1007/s00701-002-0936-3. PMID: 12111484.
36. Hashimoto M, Ishikawa M, Mori E, Kuwana N; Study of INPH on neurological improvement (SINPHONI). Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-

based scheme: a prospective cohort study. CerebrospinalFluid Res. 2010 Oct31;7:18. doi: 10.1186/1743-8454-7-18. PMID: 21040519; PMCID: PMC2987762.

37. Matsuoka T, Akakabe M, Iida JI, Kawahara M, Uchiyama Y. Changes in Cognitive Function Scores After Cerebrospinal Fluid Tap Testing in Patients with Suspected Idiopathic Normal-Pressure Hydrocephalus. CognBehavNeurol. 2018 Dec;31(4):201-206. doi: 10.1097/WNN.0000000000000176. PMID: 30562229.
38. Ko PW, Lee HW, Kang K. Frontal Assessment Battery and Cerebrospinal Fluid Tap Test in Idiopathic Normal-Pressure Hydrocephalus. Eur Neurol. 2017;77(5-6):327-332. doi: 10.1159/000472712. Epub 2017 May 5. PMID: 28472801.
39. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991 Feb;39(2):142-8. doi: 10.1111/j.1532-5415.1991.tb01616.x. PMID: 1991946.
40. Petrella G, Czosnyka M, Smielewski P, Allin D, Guazzo EP, Pickard JD, Czosnyka ZH. In vivo assessment of hydrocephalus shunt. Acta Neurol Scand. 2009 Nov;120(5):317-23. doi: 10.1111/j.1600-0404.2009.01176.x.Epub 2009 May 20. PMID: 19456302.
41. Eide PK, Brean A. Intracranial pulse pressure amplitude levels determined during preoperative assessment of subjects with possible idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien). 2006 Nov;148(11):1151-6; discussion 1156. doi: 10.1007/s00701-006-0896-0. Epub 2006 Oct 16. PMID: 17039303.
42. Anile C, De Bonis P, Albanese A et al. Selection of patients with idiopathic normal-pressure hydrocephalus for shunt placement: a single institution experience. J Neurosurg 2010; 113:64-73.
43. Skalický P, Mládek A, Vlasák A, De Lacy P, Beneš V, Bradáč O. Normal pressure hydrocephalus-an overview of pathophysiological mechanisms and diagnostic procedures. Neurosurg Rev. 2020 Dec;43(6):1451-1464. doi: 10.1007/s10143-019-01201-5. Epub 2019 Nov 8. PMID: 31705404.
44. Boon AJ, Tans JT, Delwel EJ et al. Dutch normal pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. J Neurosurg 1997; 87:687-93.
45. Dehvel EJ, de Jong DA, Avczaac CJ. The prognostic value of clinical characteristics and parameters of cerebrospinal fluid hydrodynamics in shuncing for idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien) 2005; 147:1037-42
46. Malm J, Jacobsson J, Birgander R et al.al. Reference values for CSF outflow resistance and intracranial pressure in healthy elderly. Neurology 2011; 76:903-9.

47. Meier U, Mutze S: Correlation between decreased ventricular size and positive clinical outcome following shunt placement in patients with normal-pressure hydrocephalus. J Neurosurg 100:1036–1040, 2004

48. Meier U, Paris S, Gräwe A, Stockheim D, Hajdukova A, Mutze S: Is there a correlation between operative results and change in ventricular volume after shunt placement? A study of 60 cases of idiopathic normal-pressure hydrocephalus. Neuroradiology 45:377–380, 200

49. Bradley WG Jr. Idiopathic normal pressure hydrocephalus: new findings and thoughts on etiology. Am J Neuroradiol 2008; 29:1-3. 133

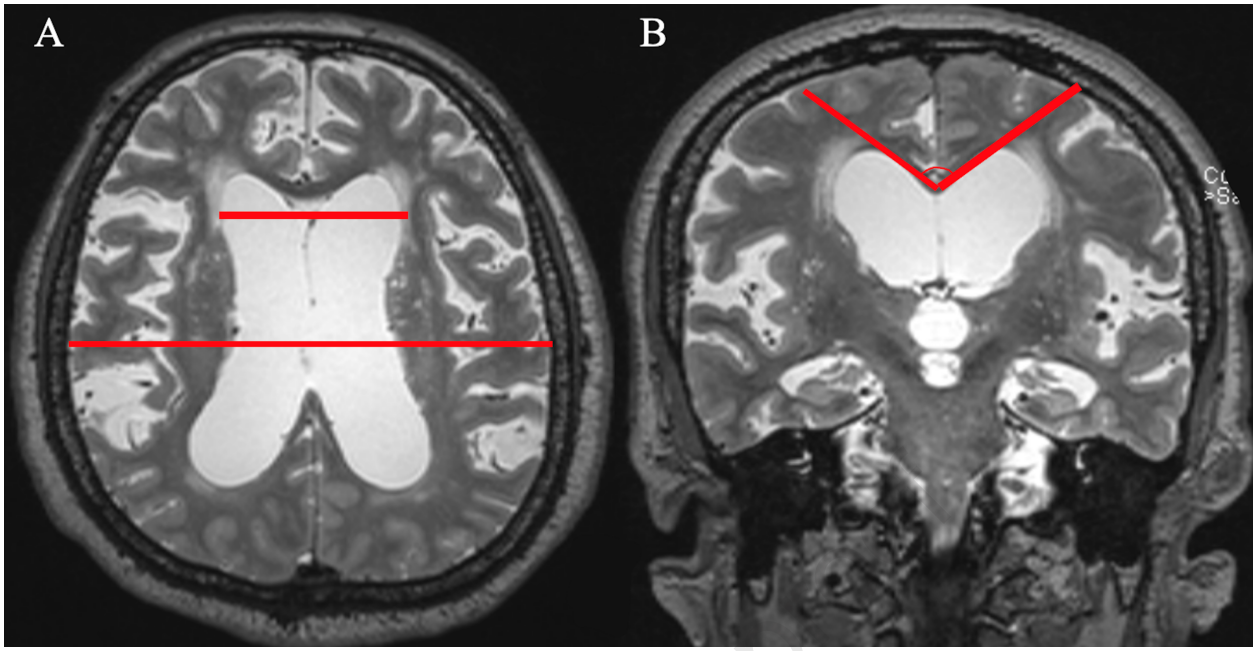
50. Scollato A, Gallina P, Gautam B et al. Changes in aqueductal CSF stroke volume in shunted patients with idiopathic normal-pressure hydrocephalus. Am J Neuroradiol 2009; 30:1580-6.

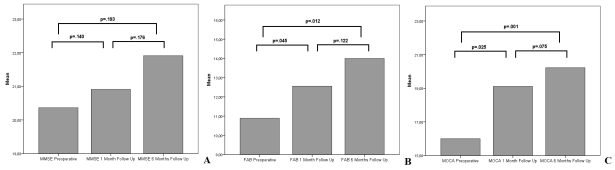
51. Krauss JK, Regel JP, Vach W, Jüngling FD, Droste DW, Wakhloo AK. Flow void of cerebrospinal fluid in idiopathic normal pressure hydrocephalus of the elderly: can it predict outcome after shunting? Neurosurgery. 1997 Jan;40(1):67-73; discussion 73-4. doi: 10.1097/00006123-199701000-00015. PMID: 8971826.

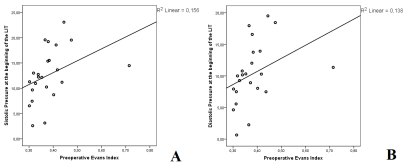
52. Hurley RA, Bradley WG Jr, Latifi HT, Taber KH. Normal pressure hydrocephalus: significance of MRI in a potentially treatable dementia. J NeuropsychiatryClinNeurosci. 1999 Summer;11(3):297-300. doi: 10.1176/jnp.11.3.297. PMID: 10440004.

Table 1 – Descriptive statistics of measured variables

	Mean	Minimum	Maximum	Std. Deviation
R^2 (1/mL)	,8868	,63	,98	,09560
Elasticity (1/mL)	,6315	,28	1,30	,23841
R_{out} [mmHg/(ml/min)]	16,8067	,00	54,39	10,20843
Mean Pressure at the Beginning of the LIT (mmHg)	11,0277	1,53	21,30	4,94107
Systolic at the Beginning of the LIT (mmHg)	12,2412	2,59	23,07	5,13192
Diastolic at the Beginning of the LIT (mmHg)	9,9442	,65	19,50	4,86050
Mean at the End of the LIT (mmHg)	28,4808	13,30	64,10	10,67918
Systolic at the End of the LIT (mmHg)	34,4692	14,35	95,82	15,48159
Diastolic at the End of the LIT (mmHg)	22,8038	11,61	42,24	7,25759







A

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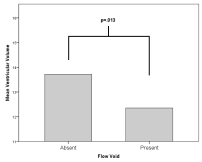

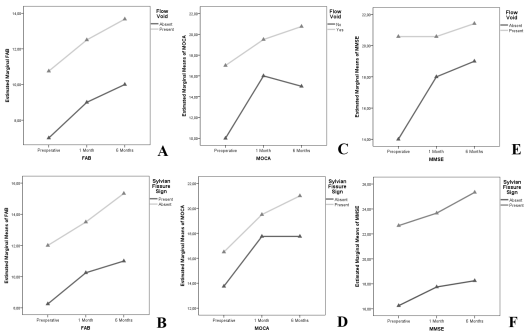

Abbreviations:

Normal Pressure Hydrocephalus (NPH); Corpus Callosum Angle (CCA), Evan's Index (EI), Transventricular Reabsorption signs – Fisher's Edema (FE); Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), Lumbar Infusion Test (LIT), Lumbar Tap Test (LTT), cerebrospinal fluid (CSF), ventriculo-peritoneal shunt (VPS), magnetization-prepared rapid acquisition gradient echo (MPRAGE); diffusion tensor sequences (DTI), Intracranial Pressure (ICP).

DISCLOSURE CONFLICT OF INTEREST

Roma, Italy 01/05/2022

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Global Neurocognitive and Frontal Functions analysis and Precision Intrathecal Pressure Measurement to Settle the Diagnostic Dilemma of the Normal Pressure Hydrocephalus: a preliminary experience.

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Alessandro Pesce: Conceptualization, formal analysis, inverstigation. **Mauro Palmieri**: formal analysis, writing, original draft and review, visualization. **Angela Scattolin**: Investigation. **Francesco Guerrini**: investigation. **Marek Czosnyka**: Supervision, writing review. **Zofia Czosnyka**: Supervision, writing review. **Massimo Marano**: investigation. **Vincenzo di Lazzaro** writing review. **Angelo Pompucci**: supervision. **Luigi Iuliano**: writing review. **Gianpaolo Petrella**: Conceptualization, writing review.