Normal pressure hydrocephalus and parkinsonism: preliminary data on neurosurgical and neurological treatment

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Normal pressure hydrocephalus and parkinsonism:
preliminary data on neurosurgical and neurological treatment

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Abstract

Objective: Idiopathic normal pressure hydrocephalus (iNPH) may present, besides the classic triad of symptoms, extrapiramidal parkinsonian like movement disorders. We present a randomized prospective study comparing adjustable ventriculo-peritoneal (VP) shunt insertion plus dopamine oral therapy (group A) versus VP shunt alone (group B) in patients affected by iNPH associated with parkinsonism.

Methods: A detailed screening process included neurological, neurosurgical and neuropsychological evaluations, followed by cerebrospinal fluid (CSF) tap test (TT) and resistance outflow (Ro) measurement. Outcome was evaluated through the Japanese NPH grading scale-revised (JNPHGSR) and the motor (third) section of the Unified Parkinson’s Disease Rating Scale (UPDRS-m). Friedman’s analysis of variance with Wilcoxon post-hoc test was used to evaluate the difference in JNPHGSR and UPDRS-m scores between pre-treatment and follow-up (12 months) in the two groups, while Kruskal-Wallis statistic and post-hoc Mann-Whitney test was used to compare the change in JNPHGSR and UPDRS-m scores between the two groups.

Results: 32/54 (59%) patients (mean age 73.2) screened in 36 months met the inclusion criteria, but only 30 were enrolled (two refused surgery), 15 in each group. Preoperative 123I-Ioflupane-cerebral SPECT (DaTSCAN) revealed striatal dopaminergic deficit in 14/30 patients (46.5%). At the final 12 months follow-up, both groups improved JNPHGSR and UPDRS-m scores. The UPDRS-m score improvement was significant in both groups, but greater in group A (p<0.003); JNPHGSR score improvement was similar in the two groups.

Conclusion: iNPH associated with parkinsonism may be a frequent finding. In these cases, patients may benefit from VP shunt plus dopamine oral therapy.

Keywords: normal pressure hydrocephalus; parkinsonism; Cerebro-spinal fluid; ventriculo-peritoneal shunt; UPDRS; DaTSCAN
Abbreviation list:

- CSF: cerebro spinal fluid
- CT: computer tomography
- DaT: dopamine transporter
- DaTSCAN: 123I-Ioflupane-cerebral SPECT
- FAB: Frontal Assessment Battery
- FDA: Food and Drug Administration
- GA: general anesthesia
- H-Y score: Hoehn-Yahr score
- ICP: intracranial pressure
- iNPH: Idiopathic normal pressure hydrocephalus
- JNPHGSR: Japanese NPH grading scale-revised
- MMSE: Mini Mental State Examination
- MODA: Milan Overall Dementia Assessment
- MR: magnetic resonance
- Ro: determination of outflow Resistance
- SD: standard deviation
- SPECT: Single photon emission computerized tomography
- TT: tap test
- TUG: Timed up and go test
- UPDRS-m: Unified Parkinson’s Disease Rating Scale, motor section
- VP shunt: ventriculo-peritoneal shunt
Introduction

Life expectancy has increased incredibly in the last 50 years in developed countries; a great achievement of medicine and health care systems but, at the same time, it represents a critical issue for 21st century physicians. The percentage of elderly patients is constantly increasing and consequently neurodegenerative diseases incidence. Hence, neurologists and neurosurgeons are facing more and more patients affected by age related diseases.

Idiopathic normal pressure hydrocephalus (iNPH) is a potentially treatable neurological disorder of the elderly. It comprises disturbances of gait and balance, urinary control, and cognition (so-called “classic triad” of symptoms of the disease) in combination with enlargement of the cerebral ventricles. Gait and balance disturbances are the most common clinical findings and may occur alone or together with cognitive and urinary symptoms. Diagnosis of iNPH is often challenging due to its varying presentation and overlapping with other disorders common in the elderly such as cerebrovascular and neurodegenerative diseases, urologic dysfunctions, lumbar stenosis, et cetera. Today, the most effective treatment offered to patients is surgical shunting with ventriculo-peritoneal shunt (VP shunt), usually with programmable valves.

Furthermore, not all patients do show the “classic triad” of symptoms; indeed, an undeniable number of patients often present signs of movement disorders, such as parkinsonism. Diagnosis and treatment become even more challenging in this group of patients and adequate management requires both the neurologist and the neurosurgeon. Up to now, these patients may be treated surgically with VP shunt or with L-dopa medications; however, there is a conspicuous lack of information concerning the outcome and, more important, the proper therapy. The incidence of this association is not clear, varying from 10% to 70% of cases in previous reports. It is reasonable to affirm that this condition is probably underestimated since the diagnosis, as mentioned above, is challenging and requires two skilled specialists.

The pathophysiology of parkinsonian symptoms in iNPH has not been conclusively understood. The abnormal pulsation of cerebro spinal fluid (CSF) flow occurring in hydrocephalus may produce...
a secondary damage to the nigrostriatal dopaminergic pathway and a down regulation of D2 receptors in the striatum and putamen.\textsuperscript{15-17} Moreover, the meso-limbic dopaminergic pathway and the ascending reticular activating system may also be injured in some cases of severe and longstanding iNPH.\textsuperscript{14}

Single photon emission computerized tomography (SPECT) of the dopamine transporter (DaT), a marker of nigrostriatal degeneration, is a recent advance in imaging that supports the clinician in the differential diagnosis of movement disorders.\textsuperscript{18-22} This technique is known as (123I-Ioflupane) SPECT or, more simply, DaTSCAN.\textsuperscript{23} DaT normally reuptakes dopamine from the synaptic cleft; 123I-Ioflupane binds to DaT in the striatum; then, DaTSCAN, represents the amount of transporter present in the striatum: this can be normal and symmetrical, asymmetrically reduced, significantly bilaterally reduced or completely absent. DaTSCAN has been approved for use in SPECT imaging in Europe since 2000. It was recently approved by the Food and Drug Administration (FDA) for the use in the United States too.\textsuperscript{23}

In such a scenario, CSF biomarkers, that reflect the ongoing pathophysiological process, might further help the comprehension of iNPH or other neurodegenerative diseases biological mechanisms.\textsuperscript{24-28}

We designed a study aiming at better clarifying the actual incidence of the association iNPH-parkinsonism and at comparing the clinical outcome between VP shunt alone and VP shunt plus oral dopaminergic therapy for patients affected by the aforementioned association.

**Materials and methods**

*Study design and inclusion/exclusion criteria:* This is a prospective randomized clinical study comparing surgical intervention with adjustable VP shunt plus dopamine oral therapy (group A) versus surgical operation alone (group B) in patients affected by iNPH associated with parkinsonism. The study lasted 48 months.
Inclusion criteria were as follows: a) age between 60 and 80. b) onset of symptoms at least 6 months before. c) diagnosis of iNPH associated with parkinsonism made cooperatively by a neurosurgeon and a neurologist at the end of a detailed screening process (described below). d) third (motor) section of the Unified Parkinson’s Disease Rating Scale (UPDRS-m) between 15 and 50 and Hoehn-Yahr (H-Y score) between 1 and 3.

Exclusion criteria were as follows: a) preexisting diagnosis of neurodegenerative diseases (e.g. Parkinson or Alzheimer disease, vascular dementia). b) pre-existing diagnosis of malignant cancer of any type. c) pre-existing diagnosis of psychiatric disease treated with drugs that may interfere with dopaminergic medications. d) pre-existing diagnosis of bowel malabsorption syndrome that may interfere or compromise dopaminergic medications effects. e) previous head or abdominal surgeries of any type. f) inability to undergo computer tomography (CT) scan, magnetic resonance (MR) scan, general anesthesia (GA) or to give informed consent for any reason.

**Diagnosis and enrollment:** These were made by 2 steps: a) clinical and radiological evaluation of the patient during outpatient clinics either by the neurosurgeon or by the neurologist with suspect of iNPH associated to parkinsonism. b) Step two consisted of a short hospital admission (usually 24-48 hours). The diagnosis of iNPH had to be confirmed through close clinical assessment, review or, if needed, execution of new radiological exams (Figure 1) and calculation of Japanese NPH grading scale-revised (JNPHGSR)\(^\text{14}\), and invasive CSF tests (intracranial pressure (ICP) measurement, tap test (TT) and determination of outflow Resistance, (Ro)), according to previous published guidelines.\(^5\) Then, parkinsonism had to be validated by the neurologist along with calculation of baseline UPDRS-m. Finally, neurocognitive tests (Mini Mental State Examination (MMSE),\(^29\) Frontal Assessment Battery (FAB),\(^30,31\) Milan Overall Dementia Assessment (MODA)\(^32\), Tinetti’s Scale\(^33\) and Timed up and go test (TUG)\(^34\) were carried out as well in order to exclude patients affected by other neurodegenerative disorders (e.g. Parkinson or Alzheimer disease, vascular dementia, et cetera).
At this stage patients were enrolled in the study, signed the informed consent and were randomized into group A or B (see above). They were discharged and were scheduled for 123I-Ioflupane-cerebral SPECT (DaTSCAN) as an outpatient and for VP shunt.

**Surgical procedure and follow-up:** A new hospital admission was organized within 4 months from enrollment.

VP shunt operation was performed in a standardized way: under GA, through a pre-coronal burr hole (usually right side) a ventricular catheter was positioned (Figure 1) and then connected to an adjustable valve (Codman-Hakim programmable valve, Codman Johnson & Johnson company, Raynham, MA, USA) and to a distal catheter that was introduced into the peritoneum running under the skin. The valve was initially regulated based on the preoperative ICP measurement, response to TT and Ro.

During VP shunt operation, CSF was collected and sent for t-tau, p-tau-181 and Aβ42 proteins dosage. Within 72 hours from surgery, group A patients began oral therapy with Levodopa/Carbidopa 100+25 mg 1+1/2 tablet 4 times daily. During the whole course of the study, patients were not allowed to assume other medications with dopaminergic or antidopaminergic activity; should these drugs have been necessary (e.g. development of psychotic disorders), the patient was then excluded.

The follow-up lasted 12 months, during which valve or Levodopa/Carbidopa dosage adjustments could be possible. At the 12 months follow-up visit the calculation of UPDRS-m was done by a different neurologist blinded as to the type of treatment administered and instructed not to investigate it. Patients were instructed as well not to give information about treatment received. Neurocognitive tests and CSF proteins dosage were repeated at the 12 months follow-up. After 12 months from VP shunt, further follow-up visits were scheduled yearly, unless the patient complained new symptoms or rapid worsening of pre-existing ones.

**Results evaluation:** This study aims to investigate the incidence of iNPH associated with parkinsonism in the patients population and to evaluate the clinical outcome 12 months after
treatment measured with the JNPHGSR and the UPDRS-m. Furthermore, neurocognitive outcome and patients’ mobility and balance were also evaluated after 12 months from treatment using neuropsychological test (MMSE, FAB, MODA), Tinetti’s Scale and TUG.

**Statistical analyses:** Friedman’s analysis of variance with Wilcoxon post hoc test was used to evaluate the differences in the JNPHGRS, UPDRS-m, MMSE, FAB, MODA, Tinetti’s scale and TUG scores between pre-treatment period and follow-up in the total sample. Mean and standard deviation (SD) of these scores at pre-treatment period and follow-up and their longitudinal change were reported for group A and group B. Friedman’s analysis of variance with Wilcoxon post hoc test was also used to evaluate the differences in the outcome measures – JNPHGRS and UPDRS-m – between pre-operative and follow-up period in group A and group B. Eventually, comparisons of the longitudinal change in the JNPHGRS and UPDRS-m between group A and group B were performed using Kruskal Wallis statistic and post-hoc Mann-Whitney test. Non-parametric tests were used due to the small size of the sample and Bonferroni adjustment was applied to reduce type 1 error for multiple comparisons. Data were analyzed with SPSS 18.0.

**Results**

**Enrollment and surgery:** In the screening phase that lasted 36 months, 54 patients were considered suitable for the study either by neurosurgeons or by neurologists and were admitted to the hospital to confirm enrollment. 32/54 (59%) patients met the inclusion criteria and were finally enrolled in the study. Actually only 30/54 (55%) patients (mean age 73.2, range 61-80; 17 males and 13 females with a M:F ratio 1.3) were included in the study, since two patients refused to undergo surgery. Therefore, 15 patients were randomized in group A and 15 in group B. Included and excluded patients are summarized in Figure 2, while pretreatment data on the 30 enrolled patients are summarized in Table 1.

Preoperative DaTSCAN revealed some striatal dopaminergic deficit in 14/30 patients (46.5%) (Figure 3), 7 in both group A and B.
Surgical mortality was 0%. As reported in Table 2, complications related to VP shunt were the following: 1 intracerebral hematoma (not requiring surgical drainage) causing seizure and slight monoparesis (arm and hand, not requiring rehabilitation); 1 case of ventricular catheter displacement that required repositioning; 2 cases of abdominal catheter displacement that required repositioning; 3 cases of igromas due to overdrainage (not requiring surgical drainage, but only valve adjustments).

**Follow-up and outcome evaluation:** All patients were evaluated at the 12 months follow-up. At the end of the study, 23/30 patients (77% overall, 13 from group A and 10 from group B) showed an improvement of the JNPHGRS score. As the threshold considered significant for the acute Levodopa challenge is represented by an improvement greater than 30%, 19/30 patients (63% overall) achieved this result: 12/15 patients of group A (80%) and 7/15 (47%) patients of group B. All 3 patients in group A who did not achieve the >30% UDPRS-m improvement had a positive DaTSCAN, while of the 8 patients of group B who did not achieve the >30% UDPRS-m improvement, 5 had a positive DaTSCAN.

Outcome data at the 12 months follow-up are summarized in Table 3.

**Statistical analyses:** Both groups of our sample showed a statistically significant improvement in the JNPHGRS, UPDRS-m, MMSE, FAB, MODA, Tinetti’s scale and TUG scores at follow-up (p<0.007) as reported in Table 4. Both group A and group B significantly improved in the JNPHGRS and UPDRS-m at follow-up (Table 5). However, the improvement in the UPDRS-m was significantly greater in group A (p=0.003) when compared to group B, while no differences were found in the JNPHGRS improvement between the two groups (Table 6).

**Discussion**

iNPH features may often overlap with other neurological pathologies common in elderly people. Parkinsonian like movement disorders may be associated with iNPH too. The exact incidence of this association is not known, but in previous reported series it is extremely variable. Therefore,
we designed a rigorous diagnostic flowchart in order to obtain a homogeneous patient population affected by iNPH associated with parkinsonism. This included the execution/repetition of radiological exams, CSF invasive studies and a comprehensive neurological, neurosurgical and neuropsychological evaluation.\textsuperscript{13}

The present prospective study provides some interesting data. First of all, it shows that the association between iNPH and parkinsonism is rather common. Following a strict diagnostic process, almost 60\% of patients screened (32 out of 54) were diagnosed to harbor this association. As expected, these patients presented a predominance of motor symptoms rather than cognitive or urinary deficits.

Although it is already known that VP shunt may be a successful treatment for both iNPH and iNPH associated with parkinsonism,\textsuperscript{14,36,37} this study is the first that investigates whether VP shunt plus oral dopaminergic therapy may further improve the patients’ outcome, especially the motor deficits. Indeed, similarly to previous literature data,\textsuperscript{14,36,37} 77\% of patients showed a general improvement in their clinical status, measured through the JNPHGRS, but, even more interesting, 19/30 patients (63\% overall) showed an improvement greater than 30\% in the UPDRS-m score; of these, 12 were in the group that received both VP shunt and dopaminergic drugs. All neurocognitive tests showed an improvement as well in both groups of patients after treatment.

Since the exact pathophysiology of parkinsonian symptoms in iNPH patients is still not clear,\textsuperscript{14-17} we enclosed in our screening process also a DaTSCAN study\textsuperscript{18-22} and the dosage (before and 12 months after treatment) of some CSF biomarkers.\textsuperscript{24-28} Concerning the value of baseline (preoperative) DaTSCAN, the question was: is baseline DaTSCAN able to predict patients’ response to treatment, or viceversa, patients with positive DaTSCAN will not improve after treatment? At present we do not have a definitive answer. Anyway, we can say that it provides an overview on how compromised the nigrostriatal system is, but it has not an absolute value in predicting the outcome; in this series, for example, there were 6 patients with positive DaTSCAN
that reached a >30% UDPRS improvement either with VP shunt alone or with VP shunt plus oral dopaminergic therapy.

Looking at neurodegenerative CSF proteins dosage, while t-tau and Aβ42 were both within normal range before and after the operation, surprisingly p-tau-181 increased to abnormal values after VP shunt. It seems therefore that t-tau and Aβ42 concentration are not influenced by treatment. Conversely, affirming that the p-tau-181 CSF dosage is surely influenced by the treatment seems fairly hazardous. To the best of our knowledge, this is the first study that compares CSF degenerative proteins before and after VP shunt; larger studied are needed to confirm and/or to discuss these findings.

Dealing with such a particular pathology, the major limitations are that it is a single center study and the patient sample is small; as a consequence, the results provided, although encouraging, should be considered as preliminary data in this field. The high percentage (59%) of cases found to harbor the association between iNPH and parkinsonism could be in part explained by the fact that the Fondazione IRCCS Istituto Neurologico C. Besta is a referral center in Italy for movement disorders. Consequently many patients with parkinsonian like symptoms are referred to this center.

Planning a multicenter study may shed more light on this disease and may lead to new advances in understanding its pathophysiology. Specifically, new stimulating data could arise concerning the role of both DaTSCAN and CFS proteins dosage.

**Conclusion**

Diagnosis of the association between iNPH and parkinsonism is challenging. A close collaboration between the neurologist and the neurosurgeon plus a strict diagnostic protocol is recommended. Indeed, this association may be present in more than half of patients with typical symptoms of these diseases. In these cases, patients may benefit from VP shunt plus dopamine oral therapy.
Legend to figures:

**Figure 1.**  
A preoperative axial T-2 weighted MR showing enlargement of lateral ventricles.  
B preoperative sagittal T-2 weighted MR; note how the corpus callosum is stretched by the hydrocephalus.  
C preoperative coronal FLAIR MR; note the mild transependimal CSF reabsorption.  
D postoperative axial CT scan after VP shunt with the ventricular catheter inserted into the right lateral ventricle through a right precoronal burr hole access.

**Figure 2.** Workflow of included and excluded patients.

**Figure 3.** DaTSCAN images.  
A example of the quantitative analysis performed in a DaTSCAN. Striatum, caudate, putamen and putamen/caudate binding ratio are reported.  
B and C examples of a negative (B) and a positive (C) DaTSCAN. Red arrows point the striatum. Note the asymmetrical reduction of the activity in the right putamen in C (white arrow). Colors indicate the amount of activity (blue: minimal; yellow: intermediate; red: maximal).
References:


Table 1. Summary of pretreatment data of the 30 patients included in the study.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Mean values</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.2</td>
<td>61-80</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1.3</td>
<td>17 M; 13 F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scale</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>JNPHGSR</td>
<td>6/12</td>
<td>4-9</td>
</tr>
<tr>
<td>UPDRS</td>
<td>27.07/108</td>
<td>21-34</td>
</tr>
<tr>
<td>H-Y score</td>
<td>2.77/5</td>
<td>2-3</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.06/30</td>
<td>23.3-30</td>
</tr>
<tr>
<td>FAB</td>
<td>14.44/18</td>
<td>8-18</td>
</tr>
<tr>
<td>MODA</td>
<td>85.69/100</td>
<td>72.7-98.2</td>
</tr>
<tr>
<td>Tinetti's scale</td>
<td>15.57/28</td>
<td>5-22</td>
</tr>
<tr>
<td>JNPHGRS post TT</td>
<td>4.53/12</td>
<td>3-7</td>
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<table>
<thead>
<tr>
<th>CSF neurodegenerative proteins dosage</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>t-tau (pg/ml)</td>
<td>380.2</td>
<td>85-1161</td>
</tr>
<tr>
<td>p-tau-181 (pg/ml)</td>
<td>45.5</td>
<td>19-235</td>
</tr>
<tr>
<td>Aβ42 (pg/ml)</td>
<td>601.73</td>
<td>213-1159</td>
</tr>
</tbody>
</table>

Legend:

M: Males; F: Females; JNPHGSR: Japanese NPH grading scale-revised; UPDRS: Unified Parkinson’s Disease Rating Scale; H-Y score: Hoehn-Yahr score; MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery; MODA: Milan Overall Dementia Assessment; TUG: Timed up and go test; TT: tap test.
Table 2. Complication rate related to VP shunt in the current series.

<table>
<thead>
<tr>
<th>Complications</th>
<th>n. of patients</th>
<th>overall percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>mortality</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>VP shunt infection</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>VP shunt malfunction</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal complication</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Ventricular catheter displacement</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal catheter displacement</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Igromas due to overdrainage</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Legend:

VP shunt: Ventriculo-peritoneal shunt
Table 3. Summary of outcome data (12 months follow-up) of the 30 patients included in the study.

<table>
<thead>
<tr>
<th>Scales</th>
<th>values</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNPHGSR</td>
<td>3,93/12</td>
<td>1-8</td>
</tr>
<tr>
<td>UPDRS</td>
<td>20,23/108</td>
<td>15-30</td>
</tr>
<tr>
<td>MMSE</td>
<td>27,58/30</td>
<td>21,3-30</td>
</tr>
<tr>
<td>FAB</td>
<td>16,01/18</td>
<td>11,3-18</td>
</tr>
<tr>
<td>MODA</td>
<td>90,50/100</td>
<td>74,7-98,2</td>
</tr>
<tr>
<td>Tinetti’s scale</td>
<td>22,10/28</td>
<td>12-28</td>
</tr>
<tr>
<td>TUG</td>
<td>19,60 s</td>
<td>11,39-37,86</td>
</tr>
<tr>
<td><strong>CSF neurodegenerative proteins dosage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-tau (pg/ml)</td>
<td>380,13</td>
<td>86-1008</td>
</tr>
<tr>
<td>p-tau-181 (pg/ml)</td>
<td>65,83</td>
<td>14-164</td>
</tr>
<tr>
<td>Aβ42 (pg/ml)</td>
<td>705,63</td>
<td>276-1168</td>
</tr>
</tbody>
</table>

Legend:

JNPHGSR: Japanese NPH grading scale-revised; UPDRS: Unified Parkinson’s Disease Rating Scale; MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery; MODA: Milan Overall Dementia Assessment; TUG: Timed up and go test.
**Table 4.** Difference between pre-treatment and follow-up test scores in the total sample, mean (SD). *p<0.007

<table>
<thead>
<tr>
<th>Scales</th>
<th>pre-treatment</th>
<th>follow-up</th>
<th>change</th>
<th>Wilcoxon’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNPHGRS</td>
<td>6.00 (±1.55)</td>
<td>3.93 (±1.74)</td>
<td>-2.07</td>
<td>p=0.000*</td>
</tr>
<tr>
<td>UPDRS-m</td>
<td>27.07 (±3.70)</td>
<td>20.23 (±3.81)</td>
<td>-6.84</td>
<td>p=0.000*</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.06 (±1.98)</td>
<td>27.58 (±2.15)</td>
<td>1.52</td>
<td>p=0.000*</td>
</tr>
<tr>
<td>FAB</td>
<td>14.44 (±3.23)</td>
<td>16.01 (±2.10)</td>
<td>1.57</td>
<td>p=0.001*</td>
</tr>
<tr>
<td>MODA</td>
<td>85.69 (±7.81)</td>
<td>90.50 (±6.07)</td>
<td>4.81</td>
<td>p=0.000*</td>
</tr>
<tr>
<td>Tinetti’s scale</td>
<td>15.57 (±4.58)</td>
<td>22.10 (±4.51)</td>
<td>6.53</td>
<td>p=0.000*</td>
</tr>
<tr>
<td>TUG</td>
<td>23.24 (±9.09)</td>
<td>19.60 (±6.81)</td>
<td>-3.64</td>
<td>p=0.002*</td>
</tr>
</tbody>
</table>
Table 5. Pre-treatment and follow-up test scores in group A and group B, mean (SD). *p<0.025

<table>
<thead>
<tr>
<th>Scales</th>
<th>pre-treatment</th>
<th>follow-up</th>
<th>change</th>
<th>Wilcoxon’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNPHGRS (Gr. A)</td>
<td>6.13 (±1.51)</td>
<td>4.00 (±1.89)</td>
<td>-2.13</td>
<td>p=0.001*</td>
</tr>
<tr>
<td>JNPHGRS (Gr. B)</td>
<td>5.87 (±1.64)</td>
<td>3.87 (±1.64)</td>
<td>-2.00</td>
<td>p=0.005*</td>
</tr>
<tr>
<td>UPDRS-m (Gr. A)</td>
<td>28.53 (±3.89)</td>
<td>19.40 (±3.30)</td>
<td>-9.13</td>
<td>p=0.001*</td>
</tr>
<tr>
<td>UPDRS-m (Gr. B)</td>
<td>25.60 (±2.95)</td>
<td>21.07 (±4.22)</td>
<td>-4.53</td>
<td>p=0.007*</td>
</tr>
<tr>
<td>MMSE (Gr. A)</td>
<td>25.86 (±1.45)</td>
<td>27.93 (±1.60)</td>
<td>2.07</td>
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</tr>
<tr>
<td>MMSE (Gr. B)</td>
<td>26.27 (±2.43)</td>
<td>27.23 (±2.60)</td>
<td>0.96</td>
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</tr>
<tr>
<td>FAB (Gr. A)</td>
<td>13.84 (±3.49)</td>
<td>15.90 (±1.99)</td>
<td>2.06</td>
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</tr>
<tr>
<td>FAB (Gr. B)</td>
<td>15.05 (±2.93)</td>
<td>16.12 (±2.27)</td>
<td>1.07</td>
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<tr>
<td>MODA (Gr. A)</td>
<td>83.38 (±8.49)</td>
<td>90.12 (±5.97)</td>
<td>6.74</td>
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</tr>
<tr>
<td>MODA (Gr. B)</td>
<td>87.99 (±6.56)</td>
<td>90.87 (±6.35)</td>
<td>2.88</td>
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<tr>
<td>Tinetti’s scale (Gr. A)</td>
<td>14.33 (±5.31)</td>
<td>21.20 (±4.40)</td>
<td>6.87</td>
<td></td>
</tr>
<tr>
<td>Tinetti’s scale (Gr. B)</td>
<td>16.80 (±3.47)</td>
<td>23.00 (±4.58)</td>
<td>6.20</td>
<td></td>
</tr>
<tr>
<td>TUG (Gr. A)</td>
<td>24.04 (±11.43)</td>
<td>19.94 (±6.82)</td>
<td>-4.10</td>
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<tr>
<td>TUG (Gr. B)</td>
<td>22.44 (±6.26)</td>
<td>19.26 (±7.02)</td>
<td>-3.18</td>
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</tr>
</tbody>
</table>
Table 6. Differences in JNPHGRS and UPDRS-m change between group A and group B, mean (SD). *p<0.05

<table>
<thead>
<tr>
<th>Scores</th>
<th>Group A</th>
<th>Group B</th>
<th>Mann-Whitney test</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNPHGRS change</td>
<td>-2.13 (±1.51)</td>
<td>-2.00 (±1.69)</td>
<td>p=0.765</td>
</tr>
<tr>
<td>UPDRS-m change</td>
<td>-9.13 (±3.25)</td>
<td>-4.53 (±4.58)</td>
<td>p=0.003*</td>
</tr>
</tbody>
</table>
Figure 2

Patients suitable for the study (N=54)

Patients not enrolled in the study:
Patients with a good response to the TT and positive Ro measurement but not affected by parkinsonism (N=7)

Patients not enrolled in the study:
Patients whose symptoms did not improve with TT (N=8)

Patients not enrolled in the study:
Patients with only slight improvement after TT and negative measurement of Ro (N=4)

Patients not enrolled in the study:
Patients with a very compromised cognitive status without significant motor deficit or patients not suitable to undergo GA (N=3)

Patients enrolled in the study (N=32)

Patients excluded since they refused surgery (N=2)

Patients included in the study (N=30)

Patients enrolled in the study:
Patients with a good response to the TT and positive Ro measurement but not affected by parkinsonism (N=7)

Patients not enrolled in the study:
Patients whose symptoms did not improve with TT (N=8)

Patients not enrolled in the study:
Patients with only slight improvement after TT and negative measurement of Ro (N=4)

Patients not enrolled in the study:
Patients with a very compromised cognitive status without significant motor deficit or patients not suitable to undergo GA (N=3)

Patients excluded since they refused surgery (N=2)

Patients included in the study (N=30)
A

<table>
<thead>
<tr>
<th></th>
<th>right</th>
<th>left</th>
<th>total</th>
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<tbody>
<tr>
<td>binding ratio of striatum:</td>
<td>1.30</td>
<td>1.27</td>
<td>1.29</td>
</tr>
<tr>
<td>binding ratio of caudate:</td>
<td>1.51</td>
<td>1.27</td>
<td>1.39</td>
</tr>
<tr>
<td>binding ratio of putamen:</td>
<td>1.20</td>
<td>1.38</td>
<td>1.29</td>
</tr>
<tr>
<td>putamen/caudate binding ratio:</td>
<td>0.79</td>
<td>1.08</td>
<td>0.93</td>
</tr>
</tbody>
</table>

B

C

(Images of brain scans showing regions and ratios indicated in the table.)
Normal pressure hydrocephalus and parkinsonism: preliminary data on neurosurgical and neurological treatment

**Highlights**

- iNPH patients may present, besides the classic triad of symptoms, extrapyramidal parkinsonian like movement disorders.
- Diagnosis of iNPH associated with parkinsonism requires the close collaboration between the neurologist and the neurosurgeon.
- Patients affected may benefit from VP shunt plus dopamine oral therapy.
- DaTSCAN and CSF neurodegenerative proteins dosage might further help in understanding the pathophysiology of this association.
The Authors declare that they do not have any financial or other interests that might be construed as a conflict of interest.