Current Updates on Idiopathic Normal Pressure Hydrocephalus

Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is one of the neurodegenerative diseases which can be treated surgically with favorable outcome. The gait disturbance, cognitive, and urinary symptoms are known as the clinical triad of iNPH. In this review, we have addressed the comorbidities, differential diagnoses, clinical presentations, and pathology of iNPH. We have also summarized the imaging studies and clinical procedures used for the diagnosis of iNPH. The treatment modality, outcomes, and prognosis were also discussed.

Keywords: Diagnostic methods, idiopathic normal pressure hydrocephalus, neuro-degenerative disease, surgical management

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is commonly seen in the aging population. It is usually underdiagnosed as some of the presenting symptoms and signs have been perceived as part of the aging processes. It represents a rare cause of reversible neurological condition. The gait disturbance, cognitive and urinary symptoms are known as the clinical triad of iNPH. Dilated lateral ventricles or known as ventriculomegaly is one of the neuroradiological features. This feature however is not specific and can be found in various neurodegenerative and vascular conditions. Since it has been usually underdiagnosed, the actual worldwide incidence and prevalence have not been defined. The crude prevalence of iNPH in Japan is estimated at 10.2 in 100,000 population in 2012. The figure was higher at 31.4 in 100,000 population in those age above 60-year-old. The median annual incidence of 1.58 (ranging between 0.8 and 4.5) iNPH patients per 100,000 population in another study.

Co-Morbidities

Hypertension (40%–50%), diabetes mellitus (17%–23%), Alzheimer’s disease (AD) (14.8%), and hyperlipidemia (13.5%) are commonly found in patients with iNPH.[2,3] Patients with comorbidities of hyperlipidemia and diabetes mellitus were at two times higher odds to suffer from iNPH compared to normal population.[4] The same study also found that obesity (Odds ratio [OR] 5.428; 95% confidence interval [CI] 2.502–11.772), and psychosocial factors (OR 5.343; 95% CI 3.219–8.868) were found to be independently associated with INPH.[4] Other comorbidities include stroke and heart disease.[5]

Differential Diagnosis

Parkinsonism represents 40% of iNPH mimics and 20% of possible or probable iNPH according to standardized diagnostic criteria.[6] The increased prevalence of parkinsonism in patients with iNPH mimics suggestive of underlying neurodegenerative disease especially in the absence of significant white matter changes.[7] Patients who are diagnosed as vascular parkinsonism (VP) but with radiological evidence of ventricular enlargement (REVE) may represents the clinical spectrum of iNPH.[8] The study showed that most of the patients with clinical characteristics of VP and REVE showed elevated values of pulse wave amplitude in the cerebrospinal fluid (CSF) hydrodynamics study during the short-term monitoring of CSF pressure as observed in iNPH patients.[6]

The coexistence of AD in normal pressure hydrocephalus (NPH) is a frequent finding. However, amyloid does not seem to play a pathogenetic role in the development of cognitive deficits in NPH.[9] The study had shown that β-amyloid peptide (Aβ) 42 levels were significantly lower in NPH compared to normal population.[4] The same study also found that obesity (Odds ratio [OR] 5.428; 95% confidence interval [CI] 2.502–11.772), and psychosocial factors (OR 5.343; 95% CI 3.219–8.868) were found to be independently associated with INPH.[4] Other comorbidities include stroke and heart disease.[5]

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than in control patients, with no significant differences between AD and NPH.\(^{[6]}\) On the contrary, t-tau and p-tau levels were significantly lower in NPH than in AD, with no differences between NPH and controls.\(^{[8]}\) NPH patients with pathological Aβ 42 levels did not perform worse than NPH patients with normal Aβ 42 levels in any cognitive domains.\(^{[8]}\)

Clinical presentations

About half of the iNPH patients presented with gait disturbance without the other two symptoms.\(^{[2]}\) Those patients with mild symptoms may present with just intermittent gait problem.\(^{[9]}\) About 12%–60% of iNPH patients presented with all three symptoms.\(^{[2,10]}\) Those without the clinical triad have a different combination of presenting symptoms [Table 1].\(^{[10]}\)

Other presenting symptoms which may be due to other associated disease such as parkinsonism [Table 2].\(^{[11]}\)

Apathy represents the most common behavioral disturbance and contributes to gait disorders in iNPH.\(^{[12]}\) Other rare symptoms include oropharyngeal dysphagia,\(^{[13]}\) “falling spells”\(^{[14]}\) and impulsive aggressive behavior in both verbal and physical.\(^{[15]}\) The oropharyngeal dysphagia is due to corticobulbar tract compression by ventricular dilatation as shown in tractography analysis.\(^{[13]}\)

Pathology

Despite a subset of iNPH patients also suffer from AD, a study with brain biopsy immune-stained against amyloid-β and hyperphosphorylated tau showed AD-related brain biopsy findings were less frequent in iNPH compared to the non-iNPH patients (P < 0.05).\(^{[7]}\)

Another study had shown that allelic variation of NME8 gene was found to be statistically significant to be associated with iNPH patients compared to nondemented controls (P = 0.014).\(^{[16]}\) Furthermore, the allelic variation of NME8 gene was not related to the neuropathological changes in the brain biopsies of iNPH patients. These findings concluded that iNPH is characterized by genetic and pathophysiological mechanisms independent from AD.\(^{[16]}\) However, periventricular white matter changes (P = 0.017) were more frequent in the iNPH patients with the AA-genotype, an identified risk factor of AD.\(^{[16]}\)

Diagnostic Criteria

Idiopathic NPH is classified as confirmed iNPH, possible iNPH, and probable iNPH.\(^{[2]}\) iNPH standardized protocol at the Geneva University Hospitals involving a multispecialty team of behavioral neurologists, neurosurgeons, neuropsychologists, engineers, and physical therapists.\(^{[1]}\) Neuroimaging especially magnetic resonance imaging (MRI) plays important role in the diagnostic criteria. As iNPH is prevalence among elderly patients, generalized cerebral atrophy in imaging studies may represents chronic cerebral ischemia, which is nonspecific association with aging.\(^{[2]}\)

The concordance imaging findings of iNPH and clinical improvement following clinical tests are important before a decision is made for CSF diversion procedure.

a. Current publications on types of neuroimaging used:
   1. Evans’ index\(^{[17]}\)
   2. Callosal angles\(^{[18]}\)
   3. Magnetic resonance elastography\(^{[19]}\)
   4. Glymphatic MRI\(^{[20]}\)
   5. Hyperdynamic CSF motion\(^{[21]}\)
   6. The SILVER Index: Disproportionately enlarged subarachnoid space\(^{[22]}\)
   7. Reversed aqueductal CSF net flow\(^{[23]}\)
   8. MRI water apparent diffusion coefficient\(^{[24]}\)
   9. Arterial spin labeling perfusion MRI\(^{[25]}\)
   10. Computed tomography perfusion\(^{[26]}\)
   11. Computerized volumetric assessment of the intracranial CSF distribution\(^{[27]}\)
   12. Brain to ventricle ratios at the anterior and posterior commissure levels and three-dimensional (3D) volumetric convexity cistern to ventricle ratios\(^{[28]}\)
   13. High-field 3D-MRI study of subarachnoid space.\(^{[29]}\)

The Table 3 below summarizes the characteristics found in neuro-imaging for the diagnosis of iNPH. The net flow was in the caudocranial direction when compared with normal control which were in the opposite direction, and this was statistically significant different (P = 0.001).\(^{[23]}\) Therefore, those patients diagnosed as iNPH have hyperdynamic flow with increased velocity and volume in both systole and diastole phase.\(^{[23]}\) The reversal of net flow direction is due to the degree of rising in diastole phase exceeds that of the systole phase.\(^{[23]}\)

Brain to ventricle ratios at the anterior and posterior commissure levels and 3D-volumetric convexity cistern to ventricle ratios were useful indices for the differential diagnosis of iNPH or iNPH with Alzheimer disease from Alzheimer disease.\(^{[28]}\)

The calculated pulse pressure gradient from phase-contrast MRI-derived CSF fluid flow velocities at the level of C2 showed no correlation with pulsatile intracranial pressure.\(^{[20]}\) Therefore, this method cannot be used to substitute the invasive monitoring of pulsatile intracranial pressure in patients with iNPH considering for CSF shunting.\(^{[20]}\)

b. Current publications on various clinical procedures for the diagnosis of iNPH:
   1. CSF removal test/Tap test
      i. Improvement in the clinical symptoms\(^{[30]}\)
      ii. Association of frontal assessment battery with the gait function\(^{[31]}\)
      iii. Finger tapping and verbal fluency\(^{[32]}\)
      iv. Simultaneous quantification of cognition and gait (dual task gait assessment and mental imagery of locomotion)\(^{[31]}\)
v. Gait parameters\textsuperscript{[33]}
vi. Timed Up and Go (TUG) and its imagined version TUG\textsuperscript{[34]}
vii. Trunk sway\textsuperscript{[35]}
viii. Optic nerve sheath diameter.\textsuperscript{[16]}

2. Slow vasogenic ICP waves\textsuperscript{[37]}
3. CSF Markers
   i. Expression of hsa-miR-4274\textsuperscript{[38]}
   ii. Protein tyrosine phosphatase receptor type Q\textsuperscript{[39]}
   iii. Glycan isoforms of transferrin (Tf).\textsuperscript{[40]}
      a. “brain-type” Tf with N acetylglucosaminylated glycans
      b. “serum-type” Tf with α2,6-sialylated glycans.
4. The computer-aided intrathecal infusion test
   i. The resistance to CSF outflow.\textsuperscript{[41,42]}

The Table 4 below summarizes the clinical procedures for the diagnosis of iNPH. A retrospective study looking at the volume of CSF removed during lumbar puncture test. Log normalization of the volume of CSF removed and controlling for age and sex failed to yield a significant relationships with gait test performance. Hence, the study concluded that a higher volume of CSF removal may not be necessary in a diagnostic lumbar tap test.\textsuperscript{[43]}

A study looking at patients with NPH-like symptoms subjected to lumbar puncture, grouped into nonpatent and patent aqueduct based on high-resolution and T2-weighted 3D-MRI.\textsuperscript{[34]} The authors found that there were no differences in mean pressure or pulse amplitude during basal and plateau epochs of the lumbar infusion test in NPH patients were detected, regardless of aqueductal patency. However, rout was significantly higher in patients with patent aqueduct.\textsuperscript{[34]}

Treatment Modality of Idiopathic Normal Pressure Hydrocephalus

Shunt surgery has been established as the only durable and effective treatment for iNPH.\textsuperscript{[44]} The implantation of a ventriculoperitoneal (VP) shunt is the current standard treatment.\textsuperscript{[45]}

Types of CSF diversion procedures in iNPH patients are shown in the Table 5. A nationwide hospital-based survey in Japan done by Kuriyama et al. showed lumboperitoneal (LP) shunt was the first choice (55.1%), followed by VP shunt (43.2%) in the patient diagnosed as iNPH.\textsuperscript{[3]} A modification of VP shunt by putting the peritoneal catheter in the space between two epiploic layers of the greater omentum in iNPH patients showed favorable outcome with no significant postoperative complications.\textsuperscript{[43]}

A systematic review done by Tudor et al. found that there were no differences in the outcomes (cognition, balance, function, gait, and mobility) between ETV and standard practice (VP shunting using a nonprogrammable valve) for iNPH patients.\textsuperscript{[49]} The effectiveness of LP shunt in NPH patients were studied by Bayar et al. which found that headache was resolved in almost all patients at the 3rd month, and gait disturbance, urinary incontinence, and cognitive functions were improved by 86%, 72%, and 65% of the patients at the end of the 1st year after LP shunt surgery.\textsuperscript{[50]}

Outcomes and Prognosis

Only about 40% of the iNPH patients improved after shunt surgery, and around 60% reported their general health condition to be better than preoperatively using self-assessed modified Rankin Scale (smRS) in a study.\textsuperscript{[5]} Vascular comorbidity namely comorbidity hypertension, diabetes, stroke, and heart disease had no negative impact on the early outcome of iNPH patients following shunt surgery. However, the same study revealed patients with comorbidities of hypertension and a history of stroke had less favorable development on the smRS in long term (beyond 5 years).\textsuperscript{[5]}

| Table 1: Clinical presentations of iNPH patients |
|----------------|----------------|
| Symptom(s)       | Frequency (%)  |
| Gait disturbance only | 5              |
| Dementia only     | 2              |
| Dementia with gait disturbance | 28            |
| Urinary with gait disturbance | 4            |
| Urinary with dementia | 1             |

| Table 2: Other presenting symptoms of iNPH patients which may be due to other associated diseases such as parkinsonism |
|----------------|----------------|----------------|
| Symptom(s)       | Frequency & P值 |
| iNPH patients (n=38) (%) | Non-iNPH patients (n=130) (%) |
| Bradykinesia     | 79 & <0.001   |
| Rigidity         | 43 & <0.001   |
| Postural instability | 71 & <0.001   |
| Resting tremor   | 5 & 6         |
### Table 3: The characteristics found in neuro-imaging for the diagnosis of idiopathic normal pressure hydrocephalus

<table>
<thead>
<tr>
<th>n</th>
<th>Neuro-imaging</th>
<th>Characteristic</th>
<th>Diagnostic findings</th>
<th>Remarks</th>
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</thead>
</table>
| 1 | Axial CT of the brain | EI as marker of ventricular volume: EI ≥0.3 indicating pathologic VF\(^{[17]}\) | Cut-offs for EI to diagnose iNPH (male/female) according to age-group: (sensitivity of 80%)\(^{[17]}\) | **Remarks**
|   |                |                | 65-69 years: 0.34/0.32 | A cut-off value of 0.3 cannot be used to differentiate between normal and enlarged ventricles\(^{[17]}\) |
|   |                |                | 70-74 years: 0.36/0.33 |
|   |                |                | 75-79 years: 0.37/0.34 |
|   |                |                | 80-84 years: 0.37/0.36 |
| 2 | Coronal CT or MRI | CA was measured at the level of the midpoint of the corpus callosum, found using the mid-sagittal plane, oriented parallel to the floor of the fourth ventricle \(^{[18]}\) | Cutoff for CA to predicting response was 105.4\(^\circ\), (sensitivity of 41.5%, specificity of 87%)\(^{[19]}\) | The average CA for the entire group postoperatively (after 1 year) was 124.3\(^\circ\), which was significantly greater than this same group’s preoperative CA of 111.09\(^\circ\) (P=0.001)\(^{[20]}\) |
| 3 | MRE | Comparison between iNPH patients using MRE with normal controls to analyze alterations in parenchymal viscoelastic properties with clinical symptoms | Increased stiffness in iNPH in cerebrum, occipital and parietal (P<0.05) ROI, and decreased stiffness in periventricular ROI (P<0.01)\(^{[19]}\) | Surgical failure may suggest an alternative dementing pathology underlying the iNPH-like symptoms\(^{[19]}\) |
| 4 | Glympathic MRI | Intrathecal contrast gadobutrol enhancement and clearance in different locations were compared between iNPH and control subjects | Delayed enhancement (P<0.05), decreased clearance of gadobutrol (P<0.05) at the SF in iNPH patients\(^{[20]}\) | Method to assess human brain metabolic function and renders a potential for contrast enhanced brain extravascular space imaging\(^{[20]}\) |
| 5 | 3D-PC MRI technique | Hyperdynamic CSF motion between iNPH and normal control | Studying CSF dynamic showed pressure gradient in the Sylvian aqueduct was significantly different in patient with iNPH when compared with HC (P<0.001)\(^{[21]}\) | Patients with iNPH and AD showed similar CSF motion profiles\(^{[21]}\) |
| 6 | Axial CT of the brain | The Silver Index (DESH): ratio between the areas of the SF and the SS at the vertex | The mean value of the silver index in patients possible iNPH was 11.52±1.68 compared to 1. ±0.98 in the control group (P<0.0001)\(^{[22]}\) | The sensitivity and specificity of Silver Index were 82.8% and 96.2% respectively\(^{[22]}\) |
| 7 | MR phase-contrast-cine | To quantitatively assess the flow of CSF in the aqueduct in iNPH and HC: Vpeak, SV, MinV, Vpeak (Vpeak-s, Vpeak-d) and flow volume (Vols, Vold) of the systole and diastole | The CSF Vpeak, SV, MinV, Vpeak-d, Vols, Vold of the systole and diastole significantly increased in iNPH patients compared to normal control (P<0.05)\(^{[23]}\) | Degree of rising in diastole phase exceeds that of systole phase in iNPH resulting in the reversal of netflow direction may play a key role in the occurrence of VM in iNPH patients\(^{[23]}\) |
| 8 | MRI water ADC | FPV, region PDWM and LN in iNPH, AD, sVD | ADC
FPV: iNPH group<sVD (P=0.0009) 
PDWM: iNPH group<sVD (P=0.0052) 
LN: iNPH group>sVD (P=0.002) | Different patterns of ADC values can differentiate between AD, sVD and iNPH, even when other MRI sequences appear morphologically similar\(^{[24]}\) |
| 9 | Pseudo continuous arterial Spin-Labeling Perfusion MRI | Differences in rCP between iNPH and HC | PVWM: iNPH<HC (P<0.001)\(^{[25]}\) 
LN: iNPH<HC (P<0.001) 
Thalamus: iNPH<HC (P<0.001) | Cognitive function in patients correlated with CBF in the PVWM, cerebellum and pons (P<0.01)\(^{[25]}\) |

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Table 3: Contd...

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<th>Neuro-imaging</th>
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<tbody>
<tr>
<td>10</td>
<td>CTP</td>
<td>Preoperative CBF in the normal appearing and PVWM, the LN and the GP compared in iNPH and age-matched HI as control</td>
<td>The preoperative CBF in iNPH patients was significantly reduced in the normal appearing PVWM, LN and GP</td>
<td>After shunt diversion, CBF increased in responders in all anatomical regions by 2.5%–32% to the perfusion level of HI, but remained significantly reduced in the PVWM of nonresponders</td>
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<td>11</td>
<td>CT scans volumetric study</td>
<td>Comparison between NPH (resorption disorder) and non-NPH (BA) at the SSs and BCs (SV) and VV</td>
<td>The CSF volume in the VV was evidently greater than that in the SSs and SV in NPH patients compared with BA patients</td>
<td>The discriminant analysis enables the achievement of a high percentage of correct classification of patients to the appropriate group determined on the result of a lumbar infusion test</td>
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<tr>
<td>12</td>
<td>3D-volumetric study of iNPH +/- AD</td>
<td>Brain to ventricle ratios at the anterior and posterior commissure; CC to ventricle ratios, volume of the BC and SF</td>
<td>iNPH: Small CC, large BC and SF</td>
<td>The distribution of the SSs in the iNPH with AD group was the most deformed among these three groups</td>
</tr>
<tr>
<td>13</td>
<td>High-field 3D MRI</td>
<td>VE, SS in the Cv, BC and SF between iNPH and secondary NPH</td>
<td>iNPH: VE with large SS at the BC and SF but diminished at Cv Secondary NPH: VE with diminished SS at BC, SF and Cv (blockage of CSF drainage from the SSs)</td>
<td>Disproportionate CSF distribution in iNPH is the compensatory direct CSF communication between the inferior horn of the lateral ventricles and the ambient cistern at the choroidal fissure</td>
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</table>

3D – Three-dimensional; CT – Computed tomography; EI – Evans’ index; NPH – Normal pressure hydrocephalus; iNPH – Idiopathic NPH; MR – Magnetic resonance; MRI – MR imaging; CA – Callosal angle’s; MRE – MR elastography; ROI – Regions-of-interest; 3D-PC – 3D phase contrast; CSF – Cerebrospinal fluid; AD – Alzheimer’s disease; DESH – Disproportionately enlarged SS hydrocephalus; Vpeak – Peak velocity; SV – Stroke volume; MinV – Minute flow volume; FPV – Frontal periventricular; PDWM – Parietal deep white matter; LN – Lenticular nuclei; sVD – Sub-cortical vascular dementia; ADC – Apparent diffusion coefficient; rCP – Regional cerebral perfusion; HC – Healthy control; CBF – Cerebral blood flow; CTP – CT perfusion; PVWM – Periventricular white matter; LN – Lentiform nucleus; GP – Global parenchyma; HI – Healthy individual; BA – Brain atrophy; VV – Ventricular system; CC – Convexity cistern; BCs – Basal cisterns; SF – Sylvian fissure; VE – Ventricular enlargement; SSs – Subarachnoid spaces; Cv – Convexity; VM – Ventriculomegaly

Age (hazards ratio [HR] 1.04/year, 95% CI 1.03–1.06, P < 0.001) and type 2 diabetes mellitus (HR 1.63, 95% CI 1.23–2.16, P < 0.001) were two independent factors that associated with increased risk of death among iNPH patients. However, iNPH was protective against risk of death (HR 0.63, 95% CI 0.50–0.78, P < 0.001) when compared with a normal population. Dementia as a cause of death was more common in non-iNPH patients (27% vs. 10%, P < 0.001).

The surgical outcome deteriorates with durations after surgery. In a study, 82% demonstrated a successful response to surgery at their first postoperative follow-up. However, this declined to 75% at 1 year and 62.5% patients at their last follow-up.

Complications from Cerebrospinal Fluid Diversion Procedure in Idiopathic Normal Pressure Hydrocephalus Patients

Complications from CSF diversion procedure can be categorized as infection, shunt malfunction, subdural hygroma/hematoma, or any adverse event attributed by a change in shunt setting or surgical procedure.

A study comparing the complication rate at 3 months after VP shunt in NPH and non-NPH patients found that high Karnofsky Performance Score at admission and NPH as underlying indication significantly reduced the odds ratio for a complication.

In another retrospective study of NPH over 80-year-old of age showed no patients developed immediate CSF infection or subdural hematoma, or extended length of stay due to surgical or anesthetic complications. However, on follow-up, four patients underwent re-surgery due to underdrainage, and three patients developed delayed subdural hematoma due to trauma and two with overdrainage.

Between VP shunt and VA shunt procedures, Hung et al. found 36% of VA shunted, and 42.5% VP shunted patients experienced shunt complications. Shunt over-drainage was the most common complications (27.4% and 19.9% respectively). He found VA-shunted patients were less likely experienced shunt blockage, and shunt revision as compared to VP shunted patients, (P = 0.008 and P < 0.001, respectively). He also found cardiopulmonary and renal complications were rare in VA shunted iNPH patients.

Between VP shunt and ETV, Chan et al. found that ETV was associated with a significantly higher mortality (3.2% vs. 0.5%) and short-term complication.
Table 4: The clinical procedures for the diagnosis of idiopathic normal pressure hydrocephalus

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<th>Procedure</th>
<th>Characteristic</th>
<th>Diagnostic findings</th>
<th>Remarks</th>
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<td>1</td>
<td>CSF removal test/tap test</td>
<td>30-50 ml CSF tap is performed via lumbar</td>
<td>A positive response when there is improvement in the clinical symptoms. (Gait can be assessed quantitatively using the 3-m TUG test or the 10-m straight walk test)(^{[30]})</td>
<td>The mini-mental state examination, FAB, and/or trail-making tests are applied for the assessment of cognition(^{[30]}) There was association of FAB with the gait function suggesting similar circuits producing gait symptoms and frontal lobe functions in iNPH(^{[31]})</td>
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<td>puncture in patient with VM</td>
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<td>FAB postdiagnostic CFSTT comparing responder and nonresponder</td>
<td>Higher preoperative FAB score in CFSTT responder (10.4±3.7) than nonresponder (7.6±4.4)(^{[31]})</td>
<td>Logistic regression analysis using the FAB score as independent variable showed a significant influence of the FAB on the differential diagnosis of CSFTT responders and nonresponders ((P=0.025;) OR 1.186; 95% CI 1.022-1.377)(^{[31]})</td>
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<td></td>
<td>Finger tapping and verbal fluency post CSF tap test</td>
<td></td>
<td>Post-lumbar puncture amelioration of verbal fluency and finger tapping deficits in iNPH compared with nonneurocognitive improvement in iNPH-like group(^{[32]})</td>
<td>The test can be used to predict positive postshunt clinical outcome(^{[32]}) iNPH mimics (i.e., vascular dementia or other parkinsonian syndromes)(^{[31]})</td>
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<td>Simultaneous quantification of cognition and gait (dual task gait assessment and mental imagery of locomotion) before and 24 h after CSF tapping</td>
<td></td>
<td>Improvements seen in iNPH compared to iNPH mimics(^{[31]})</td>
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<td></td>
<td>Comparing cognitive impairment (iNPH-CI) and patients with iNPH and normal cognition, looking at gait improvement 2-4 h following STT</td>
<td>Significant improvement of gait parameters in patients without cognitive impairment following STT, but patients with iNPH-CI did not benefit from STT(^{[31]})</td>
<td>Further studies are needed to elucidate the associations of cognitive impairment and quantitative gait parameters measured early and at later time points after STT(^{[31]})</td>
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<td></td>
<td>TUG and its iTUG after CSF tapping between iNPH and its mimics</td>
<td></td>
<td>Mental imagery of locomotion was modified after CSF tapping in iNPH patients, but not in the mimics(^{[34]})</td>
<td>The test before and after CSF tapping could help to identify iNPH patients from patients with similar neurological conditions(^{[34]}) The gyroscopic system quantitatively assessed postural deficits in iNPH(^{[35]})</td>
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<td>A comparison of trunk sway was performed between HE and patients with various types of hydrocephalus VM</td>
<td>iNPH have significant higher trunk sway compared to HE in standing task, measured by body-worn gyroscopic system ((P&lt;0.001)). If compared with VM, iNPH patients had significant lower sway velocity during gait ((P&lt;0.05)). This sway velocity improved after CSF drainage(^{[35]})</td>
<td>The ONSD-V before and after STT correlated well with the clinical effects of CSF removal(^{[36]})</td>
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<td>ONSD between supine and upright positions ONSD-V before and after lumbar puncture</td>
<td>Mean prepuncture ONSD-V was significantly lower in healthy volunteers and patients with no response to CSF removal (Fisher’s test) (0.05 ± 0.14 mm [SD]) than in responsive patients (0.37 ± 0.20 mm [SD], (P&lt;0.001)). The higher the ONSD-V, the better the therapeutic effect(^{[35]})</td>
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<td>2</td>
<td>SVW</td>
<td>Time-averaged signal strength was calculated over the full recording time (ICPS mean) and over the wave periods (ICPS) following ELD and ventriculoperitoneal shunting</td>
<td>Significant association between ICPS ((P=0.014)) and ICPS mean ((P=0.022)) with NPH(^{[37]})</td>
<td>Comparison between NPH patients and non-NPH patients(^{[37]})</td>
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On multivariate analysis, ETV alone predicted increased mortality and increased length of stay when adjusted for other patient and hospital factors.[47]

Conclusion

The diagnosis of iNPH should be considered when a patient presented with relevant clinical signs and symptoms with concordance radiological findings of iNPH. The CSF tap is performed as a diagnostic test with post-tapping evaluation of clinical improvements. Patients who are diagnosed with iNPH may also suffer from other diseases such as AD, parkinsonism, and other vascular and white matter diseases. Therefore, their responses to the CSF diversion procedure may not be predicted accurately. The diagnostic criteria for iNPH should also include diagnostic tests to exclude other concomitant diseases. The declination of number of responders during the follow-up may suggest the possibility of other ongoing neurodegenerative changes which could not be altered with CSF diversion procedure alone.

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Conflicts of interest

There are no conflicts of interest.

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