

# The Significance of Cerebral Comorbidities in Idiopathic Normal Pressure Hydrocephalus



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**Received:**  June 25, 2018; **Published:**  July 05, 2018

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## Abstract

Idiopathic normal pressure hydrocephalus (INPH) is a potentially treatable geriatric disease which mostly presented with triad of cognitive, gait and sphincter symptoms. There are many papers concerning vascular co morbidities such as diabetes mellitus, hypertension, ischemic heart disease and stroke in INPH. However, few data exist about cerebral comorbidities such as Lewy body diseases, frontotemporal dementia, Alzheimer's disease and cerebral microbleeds, and their impacts on the prognosis and patient management. This mini review aims to highlight those cerebral pathologies and their associations with INPH.

**Keywords:** Alzheimer's Disease; Lewy Body Dementia; Frontotemporal Dementia; Cerebral Microbleeds; Idiopathic Normal Pressure Hydrocephalus

**Abbreviations:** AD: Alzheimer's Disease; ABETA: Amyloid Beta; BVFTD: Behavioural Variant Frontotemporal Dementia; CMBS: Cerebral Microbleeds; C9ORF72: Chromosome 9 Open Reading Frame 72; FTL: Frontotemporal Lobar Degeneration; HPTAU: Hyperphosphorylated Tau-Protein; INPH: Idiopathic Normal Pressure Hydrocephalus; LBDS: Lewy Body Diseases; MRI: Magnetic Resonance Imaging; PTS: Patients

## Introduction

Idiopathic normal pressure hydrocephalus (INPH) is a disease that has clinical core findings of gait and balance disturbances, cognitive impairment and urinary incontinence. Along with these three core symptoms, ventriculomegaly exists in patients with INPH. Its prevalence increases with age, approximately rising to 6% over 80s [1]. The main treatment is drainage of cerebrospinal fluid, so called as shunt surgery. When diagnosing INPH in line of

the guidelines [2], patients should be evaluated to have some other mimickers such as dementia with Lewy body, Alzheimer's disease, frontotemporal dementia, Parkinson's disease. However, in real life those diseases could exist as comorbidity in patients with INPH.

Parkinson's disease and dementia with Lewy bodies are parkinsonian disorders like INPH and they are collectively called as Lewy Body diseases (LBDs).

Patients with LBDs are reported to have decreased cardiac uptake shown by Iodine-123 metaiodobenzyl guanidine myocardial scintigraphy, reliably differing them from other parkinsonian disorders. In a retrospective study, seven patients were found to have abnormal myocardial scintigraphy scans in out of 21 INPH patients. The patients with abnormal myocardial scintigraphy scans were found to be younger (74vs78 years,

$p=0.03$ ), to have less severe urinary dysfunction scores (1vs2,  $p=0.05$ ) than those INPH patients with normal cardiac scans (14/21) (Table 1). Although, it was retrospective, the study was important to remind that some LBDs patients might also have another treatable parkinsonian disease, namely INPH, and that the patients with INPH should be screened carefully during their follow-up period before and after shunt surgery. Besides, a study can be designed to investigate whether outcome of the treatment is affected in INPH patients suffering from comorbid LBDs.

Cerebral microbleeds (microhemorrhages) (CMBs) are another cerebral pathology that has been reported to be comorbid to INPH. CMBs are associated with cognitive decline, gait impairment, geriatric psychiatric syndromes and hypertension [3]. Indeed, they are iron deposits in the brain seen on blood-sensitive magnetic resonance imaging (MRI) sequences that are associated pathologically with hemosiderin-laden macrophages. The pathology was also reported to be presented in 83% of patients with recurrent intracerebral hemorrhages [4]. A recently interesting study showed that almost half of the patients with INPH had two or more CMBs, whereas it was 10% in healthy controls [5]. Although the study had limitations of having healthy controls with a mean age of 40 and very small number of patients with INPH (Table 1), this study supported part of vascular pathophysiological component in INPH.

**Table 1:** Cerebral comorbidities to Idiopathic normal pressure hydrocephalus (INPH).

Study	Country	Participants	Features of the outcome
Johansson et al. [5]	Sweden	Retrospective case control study	14 INPH (mean age:76.4) 41 controls (mean age:40)≥2 CMBs were in 43% vs 10%. respectively
Odagiri et al. [18]	Japan	Retrospective study	21 pts with INPH. who had I-123 myocardial scintigraphy. with symptoms of suggestive of LBDs in out of 127 patients with INPH; 5.5% of them were found to have comorbid LBDs
Korhonen et al. [7]	Finland	Case report	A 59 year-old woman with bvFTD had come up with symptoms suggestive of INPH. Her first MRI performed one year after the symptoms was compatible with INPH.
Hamilton et al. 2010 [12]	USA	Prospective	Twenty five (67.6%) of 37 INPH pts had AD-related brain biopsy pathology
Elobeid et al. [13]	Sweden	Prospective	52 (47% ) of 111 possible INPH pts had AD-related biopsy pathology
Bech-Azeddine et al. [14]	Danish	Prospective	28 patients with shunted INPH; mean age 64;25% had biopsy proven AD.
Pyykkö et al. [19]	Finland	Retrospective large cohort	AD-related brain biopsy pathology was found in 8.5% of 283 pts with INPH
Kuriyama et al. [20]	Japan	Nationwide hospital-based survey	14.8% of all pts (n=1524) had comorbid AD

Another potential comorbidity to INPH is behavioral variant frontotemporal dementia (bvFTD). It is the most common type of frontotemporal lobar degeneration (FTLD), presenting with personality changes, apathy, disinhibition, loss of empathy and insight, hyperorality [6]. As genetic factors are well known key players in the disease, a woman with non-coding region of the chromosome 9 open reading frame 72 (C9ORF72) repeat expansion-associated bvFTD was presented with INPH about one year after the first symptoms of bvFTD [7]. Her gait and balance symptoms, in particular walking speed and ability to move, improved prominently after shunt surgery and it was still observed at the 12-month evaluation. Apart from vascular component in the pathophysiology of INPH, a genetic component may also have a role along with previous reports [8,9] and the genetic predisposition deserves to be focused in further studies.

The most common neurodegenerative disease comorbid to INPH might be Alzheimer's disease [10-13], possibly due to increasing prevalence with aging of both diseases. Neuropathological studies showed amyloid beta (Aβeta) plaques and hyperphosphorylated tau-protein (HPTau) tangles, AD-related brain biopsy findings [12-14]. The effect of co morbid AD to INPH on the short and long term shunt surgery outcome had been studied. There are encouraging studies showing that gait speed, gait quality, psychomotor speed, attention, overall cognitive function, urination improved in patients with INPH after shunt surgery irrespective of the presence of AD pathology [15-17].

Aβeta and HPTau pathology in the frontal cortical biopsy of shunted INPH patients was also found not to have a negative influence on the discrepancy between postoperative improvement measured by physicians and health related quality of life reported by patient at one year after the shunt surgery. In other words, pathological findings of AD have no effect on low scores in patient's self-evaluation of health related quality of life despite having a favorable clinical outcome after surgery [18-20].

## Conclusion

INPH is a treatable geriatric disease. There may be cerebral comorbid conditions in INPH and they are important for clarifying the fundamental etiopathology of INPH. On the other hand, we should not overlook the diagnosis or preclude the treatment of another treatable disease, INPH, in case of progressive neurodegenerative diseases such as Alzheimer's disease, frontotemporal dementia or lewy body diseases.

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ISSN: 2574-1241

DOI: [10.26717/BJSTR.2018.06.001340](https://doi.org/10.26717/BJSTR.2018.06.001340)

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