We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Clinical and Cognitive Features of Idiopathic Normal Pressure Hydrocephalus

Elena Sinforiani, Claudio Pacchetti, Marta Picascia,
Nicolò Gabriele Pozzi, Massimiliano Todisco and
Paolo Vitali

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.73273>

Abstract

Introduction: Idiopathic normal pressure hydrocephalus (iNPH) is characterized by dilated cerebral ventricles with progressive impaired gait, cognition, and urinary control. Firstly described in 1965 by Hakim and Adam, it remains largely under-diagnosed. The diagnosis is based on clinical and imaging (CT or MRI) investigations; a timely diagnosis and cerebrospinal fluid (CSF) shunt surgery has reported to be beneficial in 60 up to 80% of the cases.

Body: The severity of motor and cognitive disturbances varies widely and it can be difficult to distinguish iNPH from other neurodegenerative disorders. The cognitive and behavioral disturbances have been commonly described as “fronto-subcortical dysfunction”. However, this definition is reductive not encompassing the entire cognitive spectrum of iNPH deficits. In our sample we found an impairment in respect to healthy controls in all the neuropsychological tests, but verbal memory. We could also find a positive correlation between the severity of cognition deficit and disease progression, suggesting a common pathological mechanism.

Conclusions: iNPH can be reliably diagnosed with an organized approach. Neurologists play an essential role in the care of patients and a multidisciplinary team can improve this process. An early shunt surgery might contain the progression of the disturbances and also possibly prevent their development.

Keywords: hydrocephalus, neurodegenerative diseases, cognition, aging and dementia, neurogeriatric

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) was described for the first time in 1965 by Hakim and Adam as ventricular dilation accompanied by a progressive triad of a gait disturbance, “dementia” and incontinence. Usually gait and balance disorders appear early and are the most impressive symptoms, cognitive decline and incontinence generally appear later as the disease progresses [1].

The symptoms presented usually appear as:

- Gait disturbances as apraxia or that are commonly seen in parkinsonism (bradykinetic, magnetic and shuffling gait).
- Urinary incontinence: urinary frequency, urgency, or frank incontinence.
- Dementia: executive dysfunction, psychomotor slowing, prominent memory loss, visuo-spatial difficulties, decreased attention, apathy.

The gait disturbance is typically the earliest feature noted and is considered to be the most responsive to treatment. The primary feature is thought to resemble an apraxia of gait or a “lower body parkinsonism”. True weakness or ataxia is typically not observed. The severity of gait disorders range from mild to the wheelchair.

The urinary symptoms of NPH can present as urinary frequency, urgency, or incontinence. While incontinence can result from gait disturbance and dementia, in a study by Sakakibara and colleagues [2] 95% of patients had urodynamic parameters consistent with detrusor overactivity.

The cognitive and behavioral disturbances accompanying iNPH have been commonly described as “fronto-subcortical dysfunction”.

However, this definition is reductive not encompassing the entire cognitive spectrum of iNPH deficits. We will deal with this topic more in detail later on.

The incidence of iNPH is between 2 and 6% among people affected by any dementia condition; its occurrence is probably underestimated. Brean and Eide [3] reported a prevalence of 21.9/100,000 and an incidence of 5.5/100,000 in a Norwegian population, which are probably minimum estimates according to the authors.

A more recent epidemiological study [4] confirms this impression: the prevalence of probable iNPH has been reported to be 0.2% in subjects aged 70–79 years and 5.9% in those aged 80 years and older, respectively, without difference between men and women. Moreover, as the authors wrote: “the number of subjects with iNPH is probably much higher than the number of persons currently treated”, and since the prevalence increases with increasing age they estimate approximately that 2 million persons in Europe and 700,000 in the United States may have iNPH.

A high incidence was also reported by Iseki et al. [5] in a 10-year follow-up study of a population of 70 year olds from a rural Japanese community. A recent systematic epidemiological review [6] confirmed that this pathology is under-diagnosed.

The need for guidelines and operating criteria for the diagnosis and management of this condition was firstly implemented by the Japanese Society of Normal Pressure Hydrocephalus in 2004; as the paper however was available only in Japanese, in 2005 Marmarou et al. [7] published English language guidelines designed to be “acceptable in the United States and abroad”. Then, as there were some differences between the two guidelines, International and Japanese, in 2008 Ishikawa et al. [8] proposed an English and up to date version of the previous Japanese guidelines in order to make them known worldwide.

Finally, in 2012, given the significant increase in basic and clinical research on iNPH and the availability of more high level evidence, Mori et al. [9] published a revision of the English language version of the Japanese guidelines.

More recently, Williams and Relkin [1] have published detailed indications on the diagnosis and management of iNPH; on the basis of an extremely clinical approach, the authors stress the concept that the starting point should be a comprehensive history and neurological examination, review of neuroimaging studies, and evaluation of the differential diagnosis. Moreover, the article reports a comparison between the International and Japanese Guidelines, where the former are more exhaustive regarding the clinical features.

2. Imaging studies

In most cases of new onset of neurologic symptoms, a computerized tomography (CT) scan of the brain is initially obtained. Although magnetic resonance imaging (MRI) is more specific than CT in iNPH, a normal CT scan can exclude the diagnosis. As shown in **Figure 1** MRI findings in iNPH include the following:

- ventricular enlargement out of proportion to sulcal atrophy, with typical rounding of frontal horns
- prominent periventricular hyperintensity consistent with transependymal flow of CSF and/or leukoaraiosis
- aqueduct periventricular (or slight enlargement) to exclude congenital stenosis. A more specific sign, prominent flow void in the aqueduct, the so-called hyperdynamic aqueduct or jet sign, requires spine-echo sequences, currently dismissed in routine MRI, replaced by the faster turbo-spin-echo sequences, (Today, a confirmation of the hyperdynamic aqueduct should be obtained by measuring aqueduct cerebral spinal flow (CSF) stroke volume by phase-contrast MRI [10])
- thinning and elevation of corpus callosum on the median sagittal slice, and acute callosal angle in the coronal slice passing through the posterior commissure [11].

A narrow CSF space at the high convexity/midline areas relative to Sylvian fissure size was recently shown to correlate with a diagnosis of probable or definite iNPH. This specific sign, called “Disproportionally enlarged Subarachnoid spaces Hydrocephalus” (DESH) [12] has been found the most sensitive to the ventricular shunting. To establish a diagnosis of NPH, an

MRI or CT must show an Evans index of at least 0.3 [13]. In addition, to exclude hydrocephalus ex vacuo, one or more of the following must also be present:

- disproportionally enlarged subarachnoid spaces hydrocephalus (DESH)
- acute callosal angle
- hyperdynamic aqueduct.
- Pathophysiology

Figure 1. A: Axial FLAIR shows periventricular white matter changes, ventricles dilatation in both frontal and occipital horns, Evan's index >0.30 B: Axial FLAIR at upper level shows global sulcal thinning and focal sulcal dilatation C coronal T2 shows acute callosal angle and disproportionally enlarged subarachnoid spaces hydrocephalus (DESH) D sagittal T1 shows callosal bulging and mild aqueduct enlargement.

The pathophysiology of iNPH is still not completely understood. iNPH differs from other causes of adult hydrocephalus, in which pathological changes alter the pressure of the cerebrospinal fluid (CSF), but it is also related to alterations of the CSF dynamicity [14].

The CSF space is a dynamic system, which constantly adapts its pressure to keep it constant. It responds to changes in CSF formation or reabsorption rates, arterial and venous flow, compliance of the intracranial structures and fluctuations in intracranial pressure (ICP). This process is essential to ensure the correct functioning of the brain. Indeed, the brain is enclosed in a fixed structure and any volume increase needs to be matched by a decrease to avoid changes of the intracranial pressure and consequential functional abnormalities.

The volume of blood entering the brain varies with the cardiac cycle, being present a net intracranial inflow of blood during systole and a net outflow during diastole. Arterial supply to the brain is pulsatile while venous flow is not, and this mismatch generates transient rises in CSF pressure. The system compensates for this in two different ways. First, the blood vessels can smooth the arterial blood influx modulating their compliance. Second, the CSF flows through the cerebral aqueduct in response to pulsatile blood flow, thus maintaining intracranial pressure stable. When these processes are altered, compensatory strategies are applied. However, the compensatory mechanisms that keep the CSF pressure constant may also produce other pathological alteration [14].

In iNPH, the compliance of the system is reduced, especially in the vessel of the superior sagittal sinus [15, 16]. This lack of arterial compliance is initially countered by increased pulsatile CSF flow through the aqueduct, but as the amplitude of arterial pulsatility increases, the blood flow in systole induces large ICP pulsations, determining the 'water hammer' effect. These exaggerated pulsations cause venous damage in the periventricular region and displace the brain toward the skull [17], thus determining the development of the hydrocephalus. Indeed, hydrocephalus occurs as a result of enlarging ventricles at the expense of a reduced subarachnoid space. This is secondary to increasing pressure within the ventricles directed toward the subarachnoid space, namely as increase of the transmante pressure (i.e., the pressure gradient between the ventricles and the subarachnoid space) [17].

This pressure gradient also explains why, although there is increased intraventricular pressure, the measured opening pressure during a lumbar puncture is within normal limits. It also implies that 'normal pressure' in NPH is somewhat of a misnomer [14].

It is still unclear what triggers the initial reduction in arterial compliance. Deep white matter ischaemia surrounding arterioles may explain the loss of autoregulation [18]. When the arterioles are obstructed, venous collapse ensues, followed by impaired CSF drainage and ventricular enlargement [18].

Evidence points also to an altered cerebral blood flow (CBF), which may favor such perivascular ischemia. It has been described a strong association between impaired CBF and iNPH. Patients with iNPH are more likely to have concomitant cerebrovascular disease [19]. MRI shows increased white matter changes (WMCs) [20] and this is further supported by neuropathological studies showing microvascular alterations [21, 22]. Age-related vascular changes can

directly cause the reduction in vascular compliance [23]; this could explain the association between NPH and vascular disease.

Alternatively, it has been proposed that increased transvenular resistance in the territory of the superior sagittal sinus can act as trigger in iNPH. Indeed, it might be that the majority of CSF resorption occurs through the brain parenchyma and not at the level of the arachnoid villi or arachnoid granulations [17, 24, 25]. In this view, CSF resorption would be affected with increased transvenular resistance.

CSF outflow resistance has been investigated in few studies, which reported an abnormal outflow in animal models and subjects with in iNPH [26, 27].

More recently, the new concept of glymphatic system has been introduced [28, 29]. The glymphatic system is a macroscopic waste clearance system which utilizes a unique system of perivascular tunnels formed by astroglial cells to promote the elimination of soluble proteins and metabolites from the central nervous system. It also facilitates brain-wide distribution of several compounds including glucose, lipids, amino acids, growth factors and neuromodulators; interestingly it functions mainly during sleep. The glymphatic system has been proposed to be instrumental in normal aging and brain pathology; in particular altered glymphatic function in iNPH could possibly be a mechanism behind the high comorbidity between iNPH and Alzheimer's disease [30]. A reduced glymphatic clearance has been found in a MRI study in iNPH and interpreted as instrumental for the development of dementia in this disease [29].

Further data suggest that aquaporin-4 channels can be implicated in the pathophysiology of iNPH [31]. Aquaporin-4 channels are transmembrane proteins that facilitate water transport in the brain and play roles in fluid secretion, cell migration, brain edema, metabolism, and many aspects of cell homeostasis; a modulation of their activity could be a potential target for pharmacological management of iNPH.

Lastly, also neurodegeneration might play a role in iNPH development as suggested by the high levels of tau protein in CSF of iNPH patients [32], as detailed below.

In conclusion, there is still a debate on the different theories of iNPH pathogenesis, even if it must be stressed that these theories may not be mutually exclusive [33]. Besides the possible mechanisms, it should be stressed out that many (although not all) of the clinical symptoms are reversible if patients are early recognized and correctly treated. The fostering of an early diagnosis is a great need, but must match the clinical accuracy.

3. Diagnostic considerations

Many other illnesses can mimic iNPH and therefore have to be distinguished. Regarding in particular the motor disturbances, the most frequent disease in differential diagnosis is Parkinson's disease; start hesitation and freezing episodes can occur in iNPH similar to the gait

in Parkinson disease, however rest tremor and usually unilateral symptoms onset typical of Parkinson's disease are less commonly observed in iNPH. Furthermore, in iNPH the response to the therapy with levodopa is usually scarce. The differential diagnosis can be particularly challenging in case of vascular dementia with small vessels disease or atypical parkinsonisms, Progressive supranuclear palsy in particular [34]. The differential diagnosis with AD will be treated below.

In their paper Williams, Relkin [1] report a precise analysis of differential diagnosis. Each of the primary symptoms of iNPH has in fact multiple potential etiologies (**Table 1**). It is quite uncommon to see patients affected by only iNPH because most of them have other conditions contributing to their symptoms. On the other hand, patients without iNPH may appear to have the iNPH syndrome because of multiple comorbidities.

	Gait	Dementia	Incontinence
Disorders that may have all 3 symptoms			
iNPH, with or without comorbidities	X	X	X
Parkinsonism	X	X	X
Lewy body dementia	X	X	X
Corticobasal degeneration	X	X	X
Progressive supranuclear palsy	X	X	X
Multiple system atrophy	X	X	X
Vascular dementia	X	X	X
Neurosyphilis	X	X	X
Medication side effects	X	X	X
Multifactorial—any combination of diagnoses, with or without iNPH	X	X	X
Disorders that may have 2 symptoms			
Multifactorial—any combination of diagnoses, with or without iNPH	X	X	X
iNPH, with or without comorbidities	X	X	X
Vitamin B ₁₂ deficiency	X	X	
Cervical stenosis and myelopathy	X		X
Lumbosacral stenosis	X		X
Peripheral neuropathy	X		X
Disorders that may have only one symptom			
iNPH	X		

	Gait	Dementia	Incontinence
Degenerative arthritis of the hips, knees, ankles	X		
Spinocerebellar degeneration	X		
Peripheral vascular disease (claudication)	X		
Alzheimer dementia		X	
Frontotemporal dementia		X	
Depression		X	
Hypothyroidism		X	
Sleep apnea		X	
Prostatic hypertrophy/obstructive uropathy			X
Pelvic-floor abnormalities			X
Interstitial cystitis			X
Disorders that can aggravate other symptoms			
Visual impairment	X	X	
Hearing impairment		X	
Obesity	X		
Cardiovascular disease	X		
Pulmonary disease	X		
Chronic lower-back pain	X		
Vestibular disorders	X		

Table 1. Differential diagnosis of idiopathic normal pressure hydrocephalus (iNPH). Taken from [1].

Initially is important to identify or exclude other disorders that should be treated before evaluating iNPH. Although iNPH is described as a symptom “triad,” patients do not need to have all three symptoms. However, gait impairment is the symptom that affects nearly all patients as described by most published series and guidelines. A patient who has only dementia or incontinence should first be evaluated for other disorders. Patients with gait impairment and urinary symptoms but no cognitive impairment may need evaluation for spinal cord disorders. Although any of the primary iNPH symptoms may be the initial symptom, gait impairment is usually either the first or worst symptom.

4. Management

Even though research in this field has advanced, iNPH still has to be considered a complex pathology whose diagnosis and management continue to present many problems. The main interest is represented by the fact that iNPH can be considered a potentially reversible dementia. Surgical diversion of CSF via a shunt remains the main treatment for this condition. This is based on the presumption that CSF diversion will reduce or normalize the transmantle pressure, thereby stabilizing or improving symptoms [14].

Ventriculo-peritoneal (VP) shunts are the most commonly used [35]; in Japan iNPH is treated mainly with lumboperitoneal (LP) shunts and in the last years also in Western Countries this procedure has began to be adopted. The data are still scarce, but LP shunts seem to have effectiveness rates similar to those of VP shunts. Despite greater rates of device-related complications, LP shunting can be recommended for the treatment of patients with iNPH because of their minimal invasiveness and lack of the lethal complications seen with VP shunts [36].

It must be stressed out that not all patients with iNPH are candidate for shunt surgery. The risk-to-benefit ratio has to be assessed individually. Prior to embarking upon surgical therapy, knowing which patients may benefit from surgery is necessary. All patients with suspected iNPH should undergo diagnostic CSF removal (either large-volume lumbar puncture and/or external lumbar drainage), which has both diagnostic and prognostic value. Detailed testing is performed before and after CSF drainage; improvement in motor symptoms after large-volume drainage supports the diagnosis of iNPH, while improvement does not rule out iNPH. Recently, a novel standardized paradigm with a simultaneous quantification of cognition and gait (dual task gait assessment and mental imagery of locomotion) before and 24 h after CSF tapping has been proposed [37], which can contribute to the identification of patients with iNPH from its mimics. The same authors underline the major limitation of this paradigm (i.e. an expansive and time-consuming evaluation), however it responds to the need of standardized evaluative parameters. Moreover, a levodopa challenge may be helpful to rule out idiopathic Parkinson disease; patients with iNPH have no significant response to levodopa or dopamine agonists.

The best candidates for shunt surgery would show imaging evidence of ventriculomegaly, indicated by a frontal horn ratio exceeding 0.30 on imaging studies, with one or more of the following criteria, as indicated by Schneck [38]:

- Presence of a clearly identified etiology.
- Predominant gait difficulties with mild or absent cognitive impairment.
- Substantial improvement after CSF withdrawal (CSF tap test or lumbar drainage).
- Normal-sized or occluded sylvian fissures and cortical sulci on CT scan or MRI.
- Absent or moderate white matter lesions on MRI.

Specific criteria and guidelines have been defined for the surgical procedure and the post-operative and long-term care, including the management of complications [7, 9], even if a consensus measurement of CSF shunting outcome is still lacking [14].

Many studies have investigated the benefit of shunt surgery. Only one assessed the benefit of shunting surgery in a randomized manner and showed that, among the 14 patients included, only those with CSF shunts improved at 3 months follow-up. In particular, the patients with effective (open) shunts showed an improvement in motor and psychometric scores (30 and 23% increase, respectively) at 3 months, whereas those with placebo (ligated) shunts were unchanged. Of note, this latter group also improved after opening the shunts, although with less benefit (28 and 18%, respectively) [39]. This rate of benefit is in line with the results of a systematic review, which reported a long-term response of 29% [40]. A double-blind randomized trial on the clinical effect of different shunt valve settings was also performed [41]; improvement after shunt surgery was evident within 3 months, irrespective of valve setting.

Recent studies showed higher rates of success (around 80–90%) [42, 43]; all these outcomes must be interpreted with caution, given the lack of standardized method of comparison. Besides the possible benefit, information about the risks of complications should also be provided, since they appear to be very common [44].

The complication ratio of CSF shunt was found on average of 38%. Potential complications include infection, seizures, abdominal problems (peritonitis, perforation, volvulus, and ascites), shunt failure or blockage, shunt over-drainage and intracranial hemorrhage. The most common complication was the shunt over-drainage occurring in up to one-third of the patients within the first year [40]. Of course, the complication rates differ across centers. The Eu-iNPH study revealed a complication rate of 28% [42], while a recent study over more 230 subjects found a complication rate of less than 12% [43].

In any case, the clinical follow-up of the patients is essential. The follow-up helps the management of the complication, identifying the patients who need adjustments or revision of the shunt. Repeated brain imaging is usually performed after shunting and can support the identification and early treatment of subdural hemorrhage [14].

As previously reported, the response to levodopa/carbidopa is absent or scarce. In patients who are poor candidates for shunt surgery, repeated lumbar punctures in combination with acetazolamide may be considered [45]. Recent studies on aquaporin-4 channels suggest interesting perspectives for future pharmacological treatment of iNPH [31].

5. Cognitive impairment in iNPH

The cognitive and behavioral disturbances accompanying iNPH have been commonly described as “fronto- subcortical dementia” [46, 47]. This clinical term is used to refer to a pattern of mental decline, characterized by executive dysfunction, psychomotor slowing and mood symptoms,

especially apathy [48, 49], that is often present in patients with iNPH. However, as it will be detailed in this chapter, a wide range of other cognitive disturbances beside frontal involvement can be detected.

Boon et al. [26] in a study evaluated global cognitive functioning, memory, and attention in a large sample (101 patients), reported that iNPH patients showed severe impairment of attention and psychomotor speed.

Iddon et al. [50], on the basis of Mini-Mental State Examination (MMSE) score cutoff, divided their sample of 11 patients into two groups: demented and non-demented. By the means of neuropsychological instruments which evaluated different cognitive functions, two cognitive profiles in iNPH have been identified, one observed in patients at a less advanced disease stage, who presented isolated frontal lobe dysfunction, and the other observed in those who have reached a more advanced stage and presented severe global cognitive dysfunction. The non-demented iNPH patients obtained a worse performance on attentional tasks, thus suggesting a deficit in cognitive flexibility, similar to patients with frontal lobe excision and patients with fronto-subcortical dementia such as Parkinson's disease [51, 52], and unlike patients with AD in which frontal functions usually are spared [53].

Ogino et al. [46], in a well-controlled study, analyzed 21 patients with iNPH and 42 patients with AD, using a neuropsychological assessment investigating different cognitive domains. iNPH patients had more severe impairment of attention, psychomotor speed and calculation than those with AD, while memory function and orientation were more preserved. Impairment in frontal functions in iNPH, but not in AD, was reported also by Miyoshi et al. [54], who compared the scores recorded on the Frontal Assessment Battery (FAB), on verbal fluency subtests and on subtests of the MMSE in patients with iNPH and AD, matched for age, sex, and MMSE score.

Tarnaris et al. [47], analyzing cognitive performances of 10 patients with iNPH through a complete neuropsychological assessment (language, memory, executive functions, visuospatial abilities, and attention), confirmed that all the patients had subcortical cognitive impairment, characterized in particular by dysexecutive dysfunction and slowed mental processing.

Therefore, some studies have tried to relate the cognitive impairment in iNPH to damage the frontal lobe. The results of single photon emission computed tomography and positron emission tomography (PET) studies showed that iNPH patients mainly presented hypoperfusion of the frontal lobe [55–57].

On the basis of the finding that periventricular white matter cerebral blood flow was reduced in iNPH [56] it has been suggested that the frontal lobe dysfunction might be secondary to a disturbance of the subcortical area connecting with the frontal lobe cortex [50, 57, 58]. The relatively preserved memory and orientation functions may be explained by a lower involvement of memory systems, including the medial temporal lobe, in iNPH than in AD [46]. However, a neuroimaging study [59] demonstrated a reduction in the medial temporal volume in iNPH. Parietal regional cerebral blood flow reduction in iNPH has also been shown in other neuroimaging studies [60, 61].

On the other hand, other studies have demonstrated that patients with iNPH can be impaired in broader cognitive domains; the definition of fronto-subcortical dementia has therefore to be considered reductive, given that the cognitive deficits observed in iNPH can extend beyond executive function, attention, working memory, and episodic memory to visuo-perceptual and visuospatial functions [26, 56, 62, 63].

Saito et al. [64] evaluated 32 iNPH patients, 32 AD patients and 30 healthy elderly controls, using an extensive and comprehensive neuropsychological battery to investigate all the different cognitive domains: language, memory, executive functions, visuospatial and visuo-perceptual abilities, attention, and mental processing speed. Their results suggested that iNPH is associated with impairment in various aspects of cognition involving both frontal-executive and posterior-cortical functions, such as visuo-perceptual and visuospatial abilities. In particular, defective performances were found on the visual discrimination and visual counting tasks; visuo-perceptual and visuospatial abilities in iNPH patients were more severe than in those with AD, whereas the degree of memory impairment was comparable to that in AD patients.

The main involvement of visuospatial functions was observed also by Bugalho et al. [65]; 17 iNPH patients have been compared with 14 healthy controls and the authors suggested that visuospatial deficits, and not executive dysfunction, could be an early sign of cognitive deterioration in iNPH patients regardless of the severity of global cognitive dysfunctions.

Some studies, instead, focused on the nature of the memory deficit in order to identify a specific pattern. Walchenbach et al. [63] analyzed 51 iNPH patients, administering the MMSE and neuropsychological tests assessing both cortical (language, visuo-perceptual skills and praxis, and memory functions) and fronto-subcortical functions (mental speed, concept shifting, and abstract reasoning). They suggested that the pattern of memory deficit in iNPH is of the frontal lobe type, in which recall is disproportionately affected with respect to recognition, while in patients with AD recall and recognition are both impaired. Ogino et al. [46] observed memory impairment in iNPH, but they found that impairment of executive functions was more severe, while impairment of memory and orientation was milder in patients with iNPH than in those with AD. On the contrary, Saito et al. [64] found that both recognition and recall were impaired in a similar fashion both in iNPH and AD groups, thus suggesting that memory impairment in iNPH is not exclusively ascribable to frontal lobe dysfunction.

Therefore the data of the literature seem to confirm a wide range of cognitive decline in iNPH patients and according to Devito et al. [66] we can conclude that: "in some cases it may be qualitatively similar to normal aging, in others it may manifest as progressive dementia with gait disturbance, clinically similar to Alzheimer's or Parkinson's disease".

However, there is no general agreement on the neuropsychological instruments to be used in assessing cognitive deficits. Bugalho et al. [65] employed a cognitive assessment protocol focused on various cognitive domains (global cognitive function, verbal memory, impulse control, verbal fluency, working memory, attention, visuospatial reasoning, and visuo-constructive abilities) and also on mood and hand dexterity. Devito et al. [66] in a not recent but very interesting paper have reviewed possible application of clinical neuropsychology and

how it has contributed to our understanding of cognition in iNPH; they proposed a clinical assessment protocol in which beside cognitive evaluation a great importance was attached to the evaluation of emotional domains, apathy and depression in particular, and quality of life.

Ogino et al. [46] assessed cognitive functions by administration of the Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised, and Alzheimer Disease Assessment Scale (ADAS) orientation subtest. Saito et al. [64] used an exhaustive and detailed neuropsychological assessment, which included the MMSE for general cognitive function, Digit Span and Spatial Span for attention, Word fluency, Trail Making Test A (TMT A) and FAB for executive function, Object naming subtest for language, the Word recall and Word recognition subtests of ADAS for episodic memory and Visual discrimination, Overlapping figures and Visual counting tasks for evaluating visuoperceptual and visuospatial functions.

In a recent study by Missori and Currà [67] all the patients underwent a wide neuropsychological assessment: MMSE, FAB, Rey's 15 words immediate and delayed recall, Wisconsin Card Sorting Test, TMT, Attentive Matrices, Analogies test, and Digit Span forward and backward tasks. However, the authors included only the scores from the MMSE in the analysis of the results because the aim of their work was to grossly quantify cognitive impairment in patients.

As we can see, most authors have used large neuropsychological battery, but different measures within the single cognitive domain have been administered in the different studies. Therefore the various studies are not immediately comparable and a standardized protocol should be needed.

6. Cognitive impairment after shunt surgery

iNPH is considered a potentially reversible dementia and as described above the treatment of choice is ventriculo-peritoneal or atrial shunt device placement. When considering the global outcome, there is a general agreement about the fact that short-term results are more likely to be influenced by shunt-associated risks, while long-term results are more influenced by other factors, such as concomitant neurodegenerative and cerebrovascular diseases; the one-year post-shunt period can be considered a determinant of long-term results of the treatment [68].

Shunt surgery can help to reduce cognitive impairment, especially if it is performed during the early stage of deterioration, as it will be more detailed below; if the pressure is not relieved quickly by a shunt patients with severe iNPH will in fact develop overall cognitive impairment [9, 50]. This deterioration is only partially reversible as reported by Andrn et al. [69], who described the effects of waiting for at least 6 months before surgery and compared the outcome with that seen in patients who waited for less than 3 months. The patients of the first group significantly deteriorated; both groups ameliorated at the same size after surgery, but since the symptoms of the patients of the first group had worsened while waiting, their final outcome was significantly poorer.

Indeed, most studies report an improvement after surgery, but there is no general agreement neither about cognitive functions are more likely to be restored after shunt placement nor about possible indicators with a predictive value.

Iddon et al. [50], as already mentioned, studied 11 patients (5 demented and 6 non-demented); the demented patients showed a significant improvement after shunt surgery, whereas in the not demented patients who presented frontal deficits no improvement could be detected. The same authors suggested that even successful shunt surgery may not alleviate all aspects of cognitive impairment.

Thomas et al. [70] reported that verbal memory and psychomotor speed appear to be the functions more likely to respond to shunt surgery; 22 (53.2%) out of 42 patients at least 3 months after surgery showed an overall cognitive improvement (defined as a four-point improvement on MMSE or an improvement by 1 standard deviation in 50% of the neuropsychological tests) and a significant improvement in tests of verbal memory and psychomotor speed. However, in patients who, at baseline, presented impairment of both verbal memory and visuoconstructive functions, the cognitive improvement was less pronounced; on this basis the authors suggested that baseline cognitive scores may distinguish patients responsive to surgery, that is, the greater the impairment the smaller the recovery. Other studies report an improvement of memory, frontal lobe, and visuoconstructive functions at 6 months [71] and 1 year [62] after shunt surgery; in the paper by Mataró et al. [71] a concomitant significant increase in the global corpus callosum size on MRI was also reported.

In a series of 47 consecutive patients, Hellstrom et al. [72] reported that most of the wide range cognitive functions are typically affected in iNPH improved at 3 months after shunt placement; contrary to the study by Mataró et al. [71] the more severe functional deficits showed the greatest improvements, although they were not completely restored to the levels present in healthy controls.

Saito et al. [64] found that frontal functions (assessed using the TMT and FAB) were improved at 1 year after the shunt procedure in 26 out of 32 patients; the authors excluded that the improvement observed could be ascribed to a possible practice effect. Actually, this is an important question which can occur when patients are evaluated after a short interval of time.

Other studies have followed the patients for a longer period, identifying as outcomes the evolution toward dementia and the survival. Koivisto et al. [73] in a study with a median follow-up of 4.8 years, found an increased risk of dementia and cognitive decline even in patients who had initially responded to the shunt. At the end of the follow-up period, 117/146 (80%) had cognitive decline and 67/146 (46%) clinical dementia, mainly AD and vascular dementia. In a multivariate analysis, memory deficit as a first symptom emerged as a predictor of dementia. Interestingly, eight (5%) patients who at baseline had the full triad of symptoms presented dementia without any other signs of neurodegenerative or vascular disease.

Golz et al. [74] followed up 147 patients for 6 years after surgery through yearly examinations; 69 died during the follow-up, 61 reached the six-year assessment. Of these 61 patients, 59% had an excellent outcome, 15% satisfactory benefit, and 26% unsatisfactory results. The authors concluded that shunt surgery can be considered a safe procedure with a favorable

outcome. However, no cognitive evaluation was performed; the patients were evaluated using only a specific scale for iNPH and a Comorbidity Index to account for additional diseases, which could influence the clinical presentation and outcome.

In some studies the response to shunt has been related to the presence/absence of findings consistent with Alzheimer pathology on cortical biopsy or CSF sampling, but the results are contradictory. Golomb et al. [75] at a mean post-shunt follow-up of 4.3 months, found a small but significant improvement in tests of attention and processing speed only in patients with a cortical biopsy negative for Alzheimer pathology. These data were confirmed by Savolainen et al. [76], who studied 51 patients under 75 years of age with possible iNPH; 25 of these patients underwent shunt surgery. One year after shunt placement, 72% of the patients showed a good recovery in activities of daily living, 58% experienced improved urinary incontinence, and 57% walked better; the positive effects of the shunt were still present at 5 years. However, no change on neuropsychological test performances was found, leading the authors to conclude that neuropsychological evaluation, and the MMSE in particular, is of little value in diagnosing iNPH. Eight patients with shunt and nine without shunt died in the course of the five-year follow-up. The patients with a positive biopsy for Alzheimer pathology had worsened more than those with a negative biopsy after 1 year, but mortality was not increased in these patients.

On the contrary, Pyykko et al. [77] did not find any differences in CSF A β levels or tau biomarkers between shunt-responding and non-responding iNPH patients, the latter, however, were older; no identification of a cognitive profile was identified as no formal neuropsychological evaluation was performed in order to better define the response to shunt placement.

The same results have been obtained by Yasar et al. [78] the presence of AD pathology in 26% of the population with iNPH did not significantly influence the clinical response to shunt surgery.

Some studies have focused on the caregiver, interpreting a change of caregiver burden as an indirect sign of clinical/cognitive modification. A decrease in caregiver burden was reported by Kazui et al. [79] in the caregivers of 81 iNPH patients 1 year after the patients underwent the shunt procedure; the improvement of cognitive impairment was identified as the major factor contributing to the reduced caregiver burden, even though a formal neuropsychological evaluation was not performed.

Petersen et al. [80] evaluated the impact of shunt surgery on social function and health-related quality of life in 37 patients 6 months after the procedures; non cognitive evaluation was performed. Twenty-four (65%) showed a clinical improvement, while in 31(86%) quality of life returned almost within normal range as a consequence of their greater independence. Despite these good results, the caregiver burden was reduced only in caregivers to male patients.

In order to better understand the mechanisms underlying iNPH, some authors looked for correlations between cognitive changes and metabolic functioning in specific cerebral regions. Calcagni et al. [81] performed F-FDG PET/CT scanning 3 days before and 1 week after shunt placement in a small group of iNPH patients. After surgery the global glucose rate significantly increased in all patients, while the ventricular size did not change. Clinical status and

independence in daily life was measured using scales evaluating activities of daily living, gait, urinary incontinence, cognition (the modified Rankin scale, the Krauss scale, the Larsson categorization system, the Stein-Langfitt scale); a relationship between functional data and clinical assessment was found only after surgery, not before, while changes both in FDG uptake and in global cognitive functioning measured by MMSE were reported in 3 out of 19 subjects. A further study by the same authors [82] confirmed these data. In an earlier study, Dumarey et al. [83] observed an improvement of regional blood flow in the bilateral dorsolateral frontal and left mesiotemporal cortex in patients who had previously seen to be clinical responders to the spinal tap test. All these data show that functional changes occur early than morphological ones and seem to suggest a prompt metabolic response by neuronal cells possibly related to neuronal plasticity. As yet, however, functional imaging does not seem to provide prognostic information making it possible to identify patients who will benefit from surgery.

7. iNPH and Alzheimer's disease

As above reported iNPH can mimic other neurological diseases variously characterized by gait disturbances and cognitive impairment, namely vascular dementia with small vessel disease, dementia with Lewy bodies, Parkinson's disease and other parkinsonisms. The diagnostic differentiation can be difficult. In this regard, clinical and neuroimaging data are crucial; also the lack of response of iNPH patients to antiparkinsonian drugs can help in the diagnosis.

As regard AD, the matter is fairly complex and challenging. Motor disturbances are usually absent in AD, at least in the early stages. As for cognitive impairment, as explained in the previous section, impairment of frontal lobe-related functions is not frequent in AD, even if a "frontal" variant has been described [84]; all types of memory are impaired in AD, while recognition memory is relatively preserved in iNPH. On the other hand, an overlapping of the two diseases cannot be excluded, this is particularly important when considering the response to shunt surgery. From this perspective, many studies have tried to identify biological markers both for improving the diagnosis and predicting shunt efficacy.

Savolainen et al. [76] performed cortical biopsy in 223 iNPH patients; 66 subjects presented normal brain tissue, while Alzheimer pathology (neuritic plaques) was present in over 40% of patients. The authors suggest that these data may explain the unsuccessful recovery of many patients after shunt surgery. The presence of positive biopsies for neuritic plaques was also reported by Golomb et al. [75]; 81/117 patients with possible iNPH received a structured psychiatric interview, out of these 81, 77 were cognitively impaired (Global Deterioration Scale- GDS, ≥ 3), out of these 77, 56 received cortical biopsy. Twenty-three patients presented neuritic plaques; these subjects with positive biopsies were more cognitively impaired (higher GDS and lower MMSE scores) as well as more gait impaired than patients with negative biopsies. The prevalence of neuritic plaques increased in parallel with dementia severity from 18% for patients with GDS = 3–75% for patients with GDS scores >6 . However, in this study the concomitant Alzheimer pathology did not strongly influence the clinical response to shunt surgery independently by the severity.

On the contrary, the degree of Alzheimer pathology is reported to be important in predicting the response to surgery in the study by Hamilton et al. [85]; out of 37 patients 12 showed a negative biopsy, the remaining 25 subjects showed a high percentage (above 60%) not only of neuritic plaques but also of neurofibrillary tangles, which indicates the presence of tau pathology. Patients with moderate-to-severe A β and tau pathology showed more severe baseline cognitive impairment and poorer performance postoperatively on NPH symptom severity scales and measures of cognition, while patients with mild Alzheimer pathology responded well to shunting. The authors suggest that some patients may be relatively unimpaired by the presence of cortical Alzheimer pathology; the different results obtained in respect to previous studies are explained by the different methods employed.

Leinonen et al. [86] evaluated the predictive value of brain biopsy for the long-term outcome of iNPH in 468 patients with possible iNPH; the presence of beta-amyloid was detected in 197 (42%) patients, and together with tau pathology in 44 cases (9%), but it did not affect the survival.

On the other hand, Alzheimer pathology as neuritic plaques can be present also in the brain of normal healthy individuals [87]; therefore, in order to ameliorate the differentiation of diagnosis, also CSF biological markers have been investigated. The specific combination of both low CSF beta-amyloid (A β)-42 and elevated CSF phosphorylated tau (P-tau) in fact is considered the biological signature of Alzheimer's disease, where low A β levels reflect amyloid deposition and high tau levels indicate a prevalent non specific neuronal damage [88].

In 2007, Kapaki et al. [89] studied 85 patients subdivided in 67 with AD and 18 with iNPH, and 72 healthy controls. A β -42 levels were significantly decreased in both diseases as compared with controls, while P-tau levels were significantly increased only in Alzheimer's patients; therefore the authors concluded that P-tau may be a useful marker in the differentiation of iNPH from Alzheimer's disease.

In the same year Agren-Wilsson et al. [90] studied 62 iNPH patients, 26 patients with subcortical vascular encephalopathy and 23 healthy controls. The CSF concentration of neurofilament light protein was elevated in iNPH and vascular encephalopathy compared with the controls, levels of total tau (T-tau), P-tau, and A β -42 were lower in iNPH compared with vascular encephalopathy and controls; all markers except A β -42 were significantly elevated after shunt surgery. These results lead the authors to conclude that not a specific marker but the combined pattern of more markers can distinguish iNPH from vascular patients and controls.

Lower CSF levels of both T-tau and P-tau and amyloid precursor protein have been reported also by Jeppsson et al. [91] in 28 iNPH patients compared with 20 healthy controls, while neurofilament light protein was elevated. After surgery there was an increase; these data have been interpreted as due to a reduced periventricular metabolism and axonal degeneration rather than to a major cortical damage.

Kang et al. [92] found lower CSF A β -42 levels and lower P-tau levels in 35 iNPH patients in respect to the control reference values; tau levels correlated with gait disturbance and CSF P-tau/A β ratios were significantly higher in patients who did not respond to shunt surgery.

Jingami et al. [93] studied 55 iNPH patients, 20 Alzheimer's disease patients, 11 patients with cortico-basal syndrome, and 7 patients with spino-cerebellar degeneration. Tau levels were significantly decreased in iNPH in respect to AD especially in tap test responders patients; the authors concluded that CSF tau can be considered useful for differentiation iNPH from AD.

Pyykkö et al. [77] performed both cortical biopsy and CSF sampling in a population of 53 patients with iNPH, 26 with AD, and 23 with other diagnosis. In iNPH A β load in the brain biopsy showed a negative correlation with CSF levels of A β -42, no differences in markers of neuro-inflammation and neuronal damage were found in both iNPH and Alzheimer's patients. No differences between CSF A β levels or tau biomarkers in shunt-responding and non-responding iNPH patients have been reported, the non-responding patients were however older.

The results of a recent meta-analysis [94] suggest that iNPH may be associated with significantly reduced levels of CSF A β 42, t-tau and p-tau compared to normal controls, while compared to AD both t-tau and p-tau were significantly decreased in iNPH, but CSFA β 42 is slightly increased. The data cannot be considered definitive and helpful for the diagnosis and the authors conclude that prospective studies are needed to further assess the clinical utility of these and other biomarkers in assisting in the diagnosis of iNPH and differentiating it from AD and other neurodegenerative disorders.

Actually iNPH CSF profile seems to be different from AD, in particular most studies report low CSF tau levels which are in contrast with elevated CSF tau levels in AD. However, the results from the literature cannot be considered conclusive. With particular regard to the data pre- and post-shunt Graff-Radford [95] observe that CSF biomarkers cannot be considered helpful in distinguishing patients with iNPH from those with comorbid AD and rather can provide misleading information. The author suggests that the pre-shunt low CSF A β 42 (and other APP fragments) are not necessarily related to A β brain deposition similar to what happens in AD, but rather could be result from impaired clearance; the data of pre-shunt low tau proteins levels may have the same explanation. In iNPH in fact the brain is compressed and therefore a decrease in interstitial space and APP protein fragment drainage into the CSF may be impeded, resulting in low levels of all CSF proteins. Shunting decompresses the brain and creates more room for the interstitial space to increase and protein waste fragments to drain into the CSF; CSF proteins increase after shunting in fact has been reported. On the other hand Graff-Radford [95] remarks that this hypothesis does not exclude the hypothesis proposed by Jeppsson et al. [89] about a reduced periventricular metabolism; prospective amyloid PET studies could be needed in order to determine whether this procedure is able to distinguish iNPH from comorbid AD.

8. Our experience

As reported in our recent review [96] the classic definition "fronto- subcortical dementia" is reductive, because it cannot completely describe the entire clinical spectrum. It is now known

that patients with iNPH actually present impairment in broader cognitive domains: attention, working memory, episodic memory, visuoperceptual, and visuospatial functions [50, 63–65].

Here we report the results of our experience [97] to confirm this hypothesis. We evaluated retrospectively the cognitive profile and its relationship with disease variables in a group of subjects with iNPH. We retrospectively studied clinical charts collected from January 2010 to December 2014, at the Parkinson's Disease and Movement Disorders Unit of the Istituto Neurologico Nazionale "C. Mondino" of Pavia, Italy. A case series of 64 subjects with diagnosis of "probable" iNPH was collected. All recruited patients were referred with primary diagnoses of "parkinsonism".

The diagnosis of iNPH was made on the basis of clinical, neuropsychological and neuroimaging features [1]. In particular, as regard neuroimaging, we followed the criteria previously reported: ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evans Index >0.3) and the absence of macroscopic obstruction to CSF flow. These main aspects had to be accompanied by at least one of the following supportive features: enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy; narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface; callosal angle of 40° or more; evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination; an aqueductal or fourth ventricular flow void on MRI.

Evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus has been excluded as well as other neurologic, psychiatric, or general medical conditions sufficient to explain symptoms.

Fifty-eight healthy elderly, matched for age, sex, and education, recruited among hospitalized patients and/or patients' relatives without neurological disorder or cognitive impairment, represented the normal control group (NC). All patients and NC were examined by a neurologist and tested by a neuropsychologist.

Motor symptoms have been evaluated by the Unified Parkinson's Disease Rating Scale Part III (UPDRS III); this scale has been currently applied to measure the motor impairment due to parkinsonism and is administered by the clinician [98, 99].

The following neuropsychological tests were administered to evaluate various domains of cognition:

- Mini-Mental State Examination (MMSE): general index of cognitive functioning
- Digit Span forward, Word Span and Spatial Span (Corsi's test) tests: working memory
- Rey's 15-word test, both immediate and delayed recall: long-term verbal memory
- Logical memory test: long-term verbal memory for structured material
- Raven's Colored Matrices 47: visuospatial reasoning
- Weigl's Sorting Test: categorical abstract thinking

- Frontal Assessment Battery (FAB): fronto-executive functioning
- Attentive matrices: selective attention
- Phonological and semantic fluency: lexical magazine
- Constructive Apraxia: copying and visuospatial abilities.

Age-, gender-, and education-corrected scores were calculated from the raw scores; the corrected score then were transformed into equivalent scores, ranging from 0 (pathological) to 1 (lower limit of normal) and 2, 3, 4 (normal).

As reported in **Table 2**, compared to normal group, iNPH patients showed a worst cognitive performances in almost all neuropsychological tests, except for Rey’s 15-word test, immediate recall, and Logical memory test, which were within the normal range (ANOVA).

Test/subtest	iNPH	NC	P value
Subjects F/M	64 29/35	58 26/32	
Age (years)	73.7 ± 7.5 (range 66–81)	76.0 ± 5.8 (range 71–81)	NS
Education (years)	8 ± 5	8 ± 5	NS
Disease duration (months)	40.1 ± 31.8 (range 8–71)		
MMSE	21.8 ± 4.9	28.5 ± 1.5	0.000000001
Digit span forward	4.4 ± 0.7	5.1 ± 1.3	0.0008
Word span	3.8 ± 0.7	4.2 ± 0.9	0.01
Spatial span (Corsi’s test)	3.4 ± 1.0	5.0 ± 1.3	0.00000002
Rey’s 15-word test	31.2 ± 7.5	33.1 ± 2.4	NS
• Immediate recall	4.7 ± 3.6	7.1 ± 2.3	0.0001
• Delayed recall			
Logical Memory test	6.9 ± 4.3	8.2 ± 3.4	NS
Raven’s Colored Matrices 47	21.0 ± 6.6	25.1 ± 5.3	0.0007
Weigl’s Sorting Test	5.9 ± 2.9	7.2 ± 2.1	0.01
Frontal Assessment Battery (FAB)	11.5 ± 3.6	15.6 ± 1.8	0.00000008
Attentive matrices	34.8 ± 12.1	42 ± 6.9	0.0003
Verbal fluency:	19.9 ± 9.2	23.1 ± 4.3	0.02
• Phonological	12.1 ± 3.4	14.0 ± 2.6	0.002
• Semantic			
Constructive Apraxia	10.9 ± 2.6	12.1 ± 1.9	0.009

Table 2. Demographic and neuropsychological profiles: Comparisons between iNPH and NC groups (M ± SD) (ANOVA)].

When considering the different cognitive domains involved and on the basis of equivalent scores, we subdivided the entire iNPH population in the following subgroups:

- Group 1 (G1): 27 patients (42%) with global cognitive impairment, characterized by global deficit of cognitive functions, or anyway by widespread deficit.
- Group 2 (G2): 15 patients (24%) with typical deficit in attention and executive abilities (fronto-cortical dysfunction).
- Group 3 (G3): 11 patients (17%) with mild cognitive impairment (MCI), single domain (isolated deficit of a single cognitive domain, i.e. memory, attention, visuospatial abilities).
- Group 4 (G4): 11 patients (17%) with no cognitive impairment.

In **Table 3**, the clinical, demographic, and motor characteristics of the different groups are reported (Chi square test).

In G1 the patients were older, with significantly longer disease duration and a more severe motor impairment in respect to the other groups ($p < 0.00001$). UPDRS III total score showed significant differences between G2 versus G3 and G4 patients ($p < 0.02$ and $p < 0.0001$, respectively). No differences were found between G3 and G4 groups.

The results of this study show that, when comparing with controls, our iNPH whole population was impaired in almost all neuropsychological measures; the extent of statistical significant varied from test to test, being more pronounced in logical and executive functions. Only episodic memory was relatively preserved; these data seem to suggest that memory impairment in iNPH is generally milder in respect to the deficit in other functions, executive in particular [46].

However, when we consider the different cognitive domains involved, we can identify subgroups of patients with different cognitive profiles: about an half of the subjects (42%) in fact presented an overall diffuse impairment which can be framed as dementia of mild to moderate

	G1 Global cognitive impairment (27 pts)	G2 Fronto-cortical dysfunction (15 pts)	G3 MCI single domain (11 pts)	G4 No cognitive impairment (11pts)
Sex M/F	13/14	10/5	7/4	5/6
Age (years)	79.3 ± 1.9*	73.7 ± 7.5	70.4 ± 4.2	69.9 ± 3.2
Disease duration (months)	54.2 ± 16.8*	40.0 ± 31.0	33.3 ± 13.2	32.4 ± 11.3
UPDRS III	36.6 ± 10.0* range 47–27	26.3 ± 3.1°+ range 29–22	20.6 ± 8.4 range 29–10	21.4 ± 2.3 range 24–16

*G1 vs. G2, G3 and G4: $p < 0.00001$; °G2 vs. G3: $p < 0.02$; +G2 vs. G4: $p < 0.0001$.

Table 3. Demographic and clinical characteristics of the different iNPH groups (M ± SD) (ANOVA).

degree, out of not demented patients, only 24% was characterized by fronto-cortical dysfunction and we also found a subgroup with impairment in a single cognitive domain and even patients without any neuropsychological deficit.

Therefore our results are in agreement with the data of the literature about a wide range of cognitive pictures in iNPH [50, 63–65, 94]; in particular, the heading of “fronto-subcortical dysfunction” is reductive as it cannot completely encompass the different cognitive profiles.

The second important finding of our study is represented by a positive correlation between cognition and disease progression; in fact, though cognitive impairment may be absent in early cases, its severity undoubtedly increases with older age, disease duration and severity of motor disturbances, hypothesizing an underlying common physiopathological mechanism. In this view, as our data can suggest, an early shunt surgery could contain not only the progression of motor disturbances but also the advance of cognitive impairment in these patients.

Our sample was enrolled on the basis of the presence of gait disturbances/parkinsonism and because of these symptoms the patients were referred to our Unit; this aspect may represent a weakness of the study in term of patient’s enrollment. On the other hand it is well-known that motor disorders are the leading presentation of iNPH [1].

In this study, we have administered an exhaustive neuropsychological evaluation in order to investigate different cognitive domains; this is crucial to obtain a more detailed cognitive profile, as suggested by different authors [64–66]. In our opinion an accurate cognitive characterization before shunt is relevant in terms of outcome measures. Enrolling homogeneous population of iNPH may improve the prediction of response to shunt surgery; a longer follow-up period and a closer interaction among the different professionals are needed.

9. Conclusions

iNPH remains a complex and underestimated disease. As far cognitive impairment, this has commonly been described as fronto-subcortical dementia, but on the basis of the data of the literature we can assume that this term is reductive as it does not fully describe the different clinical pictures observed with an involvement of many other cognitive domains. Even after many years we still agree with the remarks of Iddon et al. in 1999 [50] “There may not be one single form of dementia syndrome in NPH but rather, there are varying degrees of cognitive change pre-shunt, according to the amount of permanent brain damage that has already taken place, compounded by comorbidity factors such as hypertensive cerebral small vessel disease”. Undoubtedly, many other variables differently modulate and interfere with the disease expression. Moreover, an overlap with other neurodegenerative diseases can exist; this may be a complex and prognostic issue and could partly explain both the progression of cognitive decline and the absence of amelioration after successful CSF shunt procedures. With regard to the possible overlap with AD in particular, the weight of Alzheimer pathology in iNPH patients is not clear; studies investigating possible biological markers in fact have failed to obtain conclusive results.

The great variability of clinical pictures in iNPH has to be interpreted also taking into account the role of the “cognitive reserve” phenomenon [100]; even partially, this aspect can also contribute to the differences of the response to shunt surgery.

Clinical and neuroimaging data are crucial for the diagnosis and the literature has provided guidelines and precise neuroradiological diagnostic criteria. However, there is no general agreement about the neuropsychological measures to employ in assessing the condition, as the studies reported in the literature used different cognitive tests; this aspect is obviously relevant to the post-shunt follow-up, too. The neuropsychological assessment has to include sensitive and exhaustive measures investigating the different cognitive domains; also patients’ quality of life and caregivers’ point of view have to be investigated in particular after shunt surgery in order to obtain a more global and sensitive evaluation.

Another important issue is represented by the difficulty to establish with precision the different stages in the disease. The studies reported in the literature have been conducted in patients with different disease durations and therefore with different degrees of disease severity; this makes it difficult to compare the different results and obviously the results after shunt placement may well be negatively affected in patients with more severe or longer lasting disease. In particular as regards the shunt procedure, reliable indices predictive of a good response to surgery are still lacking; in the studies analyzed different outcome measures were employed in different follow-up periods.

We can conclude that there is a need for further studies with a better standardization; longer follow-ups and closer interaction among the different professionals involved are also requested.

Author details

Elena Sinforiani^{1*}, Claudio Pacchetti², Marta Picascia², Nicolò Gabriele Pozzi²,
Massimiliano Todisco² and Paolo Vitali³

*Address all correspondence to: elena.sinforiani@mondino.it

1 Alzheimer’s Disease Assessment Unit/Laboratory of Neuropsychology, C. Mondino National Neurological Institute, Pavia, Italy

2 Parkinson’s Disease and Movement Disorders Unit, C. Mondino National Neurological Institute, Pavia, Italy

3 Neuroradiology Unit and Brain MRI 3T Mondino Research Center, C. Mondino National Neurological Institute, Pavia, Italy

References

- [1] Williams MA, Relkin NR. Diagnosis and management of idiopathic normal-pressure hydrocephalus. *Neurology Clinical Practice*. 2013;3:375-385. DOI: 10.1212/CPJ.0b013e3182a78f6b

- [2] Sakakibara R, Uchiyama T, Kanda T, Uchida Y, Kishi M, Hattori T. Urinary dysfunction in idiopathic normal pressure hydrocephalus. *Brain and Nerve*. 2008;**60**(3):233-239
- [3] Brean A, Eide PK. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. *Acta Neurologica Scandinavica*. 2008;**118**(1):48-53. DOI: 10.1111/j.1600-0404.2007.00982.x
- [4] Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelsø. Prevalence of idiopathic normal-pressure hydrocephalus. *Neurology*. 2014;**82**:1449-1454. DOI: 10.1212/WNL.0000000000000342
- [5] Iseki C, Takahashi Y, Wada M, Kawanami T, Adachi M, Kato T. Incidence of idiopathic normal pressure hydrocephalus (iNPH): A 10-year follow-up study of a rural community in Japan. *Journal of the Neurological Sciences*. 2014;**339**:108-112. DOI: 10.1016/j.jns.2014.01.033
- [6] Martin-Laez R, Caballero-Arzapalo H, Lopez-Menendez LA, Arango-Lasprilla JC, Vázquez-Barquero A. Epidemiology of idiopathic normal pressure hydrocephalus: A systematic review of the literature. *World Neurosurgery*. 2015;**87**:298-310 <https://doi.org/10.1016/j.wneu.2015.07.005>
- [7] Marmarou A, Bergsneider M, Relkin N, Klinge P, Black PM. Development of guidelines for idiopathic normal-pressure hydrocephalus: Introduction. *Neurosurgery*. 2005;**57** (3 Suppl):S1-S3
- [8] Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miyake H, Wachi A, Takeuchi T, Kazui H, Koyama H. Guidelines for management of idiopathic normal pressure hydrocephalus. *Neurologia Medico-Chirurgica (Tokyo)*. 2008;**48**(Suppl):S1-23
- [9] Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, Nakajima M, Hashimoto M, Kuriyama N, Tokuda T, Ishii K, Kaijima M, Hirata Y, Saito M, Arai H. Japanese Society of Normal Pressure Hydrocephalus. Guidelines for management of idiopathic normal pressure hydrocephalus: Second edition. *Neurologia Medico-Chirurgica (Tokyo)*. 2012;**52**(11):775-809
- [10] Bradley WG Jr. CSF flow in the brain in the context of normal pressure hydrocephalus. *AJNR. American Journal of Neuroradiology*. 2015;**36**(5):831-838. DOI: 10.3174/ajnr.A4124
- [11] Ishii K, Kanda T, Harada A, Miyamoto N, Kawaguchi T, Shimada K, Ohkawa S, Uemura T, Yoshikawa T, Mori E. Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. *European Radiology*. 2008;**18**(11):2678-2683. DOI: 10.1007/s00330-008-1044-4
- [12] Sasaki M, Honda S, Yuasa T, Iwamura A, Shibata E, Ohba H. Narrow CSF space at high convexity and high midline areas in idiopathic normal pressure hydrocephalus detected by axial and coronal MRI. *Neuroradiology*. 2008;**50**(2):117-122. DOI: 10.1007/s00234-007-0318-x

- [13] Gyldensted C. Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. *Neuroradiology*. 1977;**14**(4):183-192
- [14] Gooriah R, Raman A. Idiopathic normal pressure hydrocephalus: An overview of pathophysiology. *Clinical Features, Diagnosis and Treatment*. 2016. DOI: 10.5772/64198
- [15] Mase M, Yamada K, Banno T, Miyachi T, Ohara S, Matsumoto T. Quantitative analysis of CSF flow dynamics using MRI in normal pressure hydrocephalus. *Acta Neurochirurgica. Supplement*. 1998;**71**:350-353
- [16] Bateman GA. Vascular compliance in normal pressure hydrocephalus. *AJNR. American Journal of Neuroradiology*. 2000;**21**(9):1574-1585
- [17] Greitz D, Greitz T, Hindmarsh T. A new view on the CSF-circulation with the potential for pharmacological treatment of childhood hydrocephalus. *Acta Paediatrica*. 1997;**86**:125-132. DOI: 10.1111/j.1651-2227.1997.tb08850.x
- [18] Bradley WG. Normal pressure hydrocephalus: New concepts on etiology and diagnosis. *AJNR. American Journal of Neuroradiology*. 2000;**21**:1586-1590
- [19] Krauss JK, Droste DW, Vach W, Regel JP, Orszagh M, Borremans JJ, Tietz A, Seeger W. Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: Effect of periventricular and deep white matter lesions. *Neurosurgery*. 1996;**39**(2):292-300
- [20] Tullberg M, Jensen C, Ekholm S, Wikkelsø C. Normal pressure hydrocephalus: Vascular white matter changes on MR images must not exclude patients from shunt surgery. *AJNR. American Journal of Neuroradiology*. 2001;**22**(9):1665-1673
- [21] Akai K, Uchigasaki S, Tanaka U, Komatsu A. Normal pressure hydrocephalus. Neuropathological study. *Acta Pathologica Japonica*. 1987;**37**(1):97-110
- [22] Del Bigio MR. Neuropathological changes caused by hydrocephalus. *Acta Neuropathologica*. 1993;**85**(6):573-585
- [23] Grünewald RA. Normal pressure hydrocephalus: Pathophysiology. *Practical Neurology*. 2006;**6**:264-266
- [24] Castro ME, Portnoy HD, Maesaka J. Elevated cortical venous pressure in hydrocephalus. *Neurosurgery*. 1991;**29**:232-238
- [25] Portnoy HD, Branch C, Castro ME. The relationship of intracranial venous pressure to hydrocephalus. *Child's Nervous System*. 1994;**10**:29-35
- [26] Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, Avezaat CJ, de Jong DA, Gooskens RH, Hermans J. Dutch normal pressure hydrocephalus study: Prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *Journal of Neurosurgery*. 1997;**87**:687-693. DOI: 10.3171/jns.1997.87.5.0687
- [27] Borgesen SE, Gjerris F. The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. *Brain*. 1982;**105**:65-86

- [28] Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic system: A Beginner's guide. *Neurochemical Research*. 2015;**40**(12):2583-2599. DOI: 10.1007/s11064-015-1581-1586
- [29] Ringstad G, Vatnehoi SAS, Eide PK. Glymphatic MRI in idiopathic normal pressure hydrocephalus. *Brain*. 2017;**140**(10):2691-2705. DOI: 10.1093/brain/awx191
- [30] Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, Sabbagh MN. Frequency of Alzheimer's disease pathology at autopsy in patients with clinical normal pressure hydrocephalus. *Alzheimer's & Dementia*. 2011;**7**(5):509-513. DOI: 10.1016/j.jalz.2010.12.008
- [31] Desai B, Hsu Y, Schneller B, Hobbs JG, Mehta AI, Linninger A. Hydrocephalus: The role of cerebral aquaporin-4 channels and computational modeling considerations of cerebrospinal fluid. *Neurosurgical Focus*. 2016;**41**(3):E8. DOI: 10.3171/2016.7.FOCUS16191
- [32] Kudo T, Mima T, Hashimoto R, Nakao K, Morihara T, Tanimukai H, Tsujio I, Koike Y, Tagami S, Mori H, Nakamura Y, Tanaka T, Mori K, Takeda M. Tau protein is a potential biological marker for normal pressure hydrocephalus. *Psychiatry and Clinical Neurosciences*. 2000;**54**:199-202. DOI: 10.1046/j.1440-1819.2000.00658.x
- [33] Keong NC, Pena A, Price SJ, Czosnyka M, Czosnyka Z, Pickard JD. Imaging normal pressure hydrocephalus: Theories, techniques, and challenges. *Neurosurgical Focus*. 2016;**41**(3):E11. DOI: 10.3171/2016.7.FOCUS16194
- [34] Magdalinou NK, Ling H, Smith JD, Schott JM, Watkins LD, Lees AJ. Normal pressure hydrocephalus or progressive supranuclear palsy? A clinicopathological case series. *Journal of Neurology*. 2013;**260**(4):1009-1013. DOI: 10.1007/s00415-012-6745-6
- [35] Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N. Surgical management of idiopathic normal-pressure hydrocephalus. *Neurosurgery*. 2005;**57**(3 Suppl):S29-S39
- [36] Nakajima M, Miyajima M, Ogino I, Sugano H, Akiba C, Domon N, Karagiozov KL, Arai H. Use of external lumbar cerebrospinal fluid drainage and lumboperitoneal shunts with strata NSC valves in idiopathic normal pressure hydrocephalus: A single-center experience. *World Neurosurgery*. 2015;**83**(3):387-393. DOI: 10.1016/j.wneu.2014.08.004
- [37] Allali G, Laidet M, Armand S, Momjian S, Marques B, Saj A, Assal F. A combined cognitive and gait quantification to identify normal pressure hydrocephalus from its mimics: The Geneva's protocol. *Clinical Neurology and Neurosurgery*. 2017;**160**:5-11. DOI: 10.1016/j.clineuro.2017.06.001
- [38] Schneck M. Normale Pressure Hydrocephalus. Medscape; Updated: Jul 12, 2016
- [39] Tisell M, Tullberg M, Hellström P, Edsbacke M, Högfeldt M, Wikkelsö C. Shunt surgery in patients with hydrocephalus and white matter changes. *Journal of Neurosurgery*. 2011;**114**(5):1432-1438. DOI: 10.3171/2010.11.JNS10967
- [40] Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: A systematic review of diagnosis and outcome. *Neurosurgery*. 2001;**49**(5):1166-1184

- [41] Farahmand D, Sæhle T, Eide PK, Tisell M, Hellström P, Wikkelsö C. A double-blind randomized trial on the clinical effect of different shunt valve settings in idiopathic normal pressure hydrocephalus. *Journal of Neurosurgery*. 2016;**124**(2):359-367. DOI: 10.3171/2015.1.JNS141301
- [42] Klinge P, Hellström P, Tans J, Wikkelsø C. European iNPH multicentre study group. One-year outcome in the European multicentre study on iNPH. *Acta Neurologica Scandinavica*. 2012;**126**(3):145-153. DOI: 10.1111/j.1600-0404.2012.01676.x
- [43] Poca MA, Solana E, Martínez-Ricarte FR, Romero M, Gándara D, Sahuquillo J. Idiopathic normal pressure: Results of a prospective cohort of 236 shunted patients. *Acta Neurochirurgica. Supplement*. 2012;**114**:247-253. DOI: 10.1007/978-3-7091-0956-4_49
- [44] Stein SC, Burnett MG, Sonnad SS. Shunts in normal pressure hydrocephalus: Do we place too many or too few? *Journal of Neurosurgery*. 2006;**105**(6):815-822. DOI: 10.3171/jns.2006.105.6.815
- [45] Aimard G, Vighetto A, Gabet JY, Bret P, Henry E. Acetazolamide: An alternative to shunting in normal pressure hydrocephalus? Preliminary results. *Revue Neurologique (Paris)*. 1990;**146**(6-7):437-439
- [46] Ogino A, Kazui H, Miyoshi N, Hashimoto M, Ohkawa S, Tokunaga H, Ikejiri Y, Takeda M. Cognitive impairment in patients with idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders*. 2006;**21**(2):113-119. DOI: 10.1159/000090510
- [47] Tarnaris A, Toma AK, Pullen E, Chapman MD, Petzold A, Cipolotti L, Kitchen ND, Keir G, Lemieux L, Watkins LD. Cognitive, biochemical, and imaging profile of patients suffering from idiopathic normal pressure hydrocephalus. *Alzheimer's & Dementia*. 2011;**7**(5):501-508. DOI: 10.1016/j.jalz.2011.01.003
- [48] Larsson A, Wikkelsö C, Bilting M, Stephensen H. Clinical parameters in 74 consecutive patients shunt operated for normal pressure hydrocephalus. *Acta Neurologica Scandinavica*. 1991;**84**(6):475-482. DOI: 10.1111/j.1600-0404.1991.tb04998.x
- [49] Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 1994;**6**(4):358-370. DOI: 10.1176/jnp.6.4.358
- [50] Iddon JL, Pickard JD, Cross JJ, Griffiths PD, Czosnyka M, Sahakian BJ. Specific patterns of cognitive impairment in patients with idiopathic normal pressure hydrocephalus and Alzheimer's disease: A pilot study. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1999;**67**(6):723-732
- [51] Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia*. 1991;**29**(10):993-1006

- [52] Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Lange KW, Robbins TW. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain*. 1992;**115**(Pt 6):1727-1751
- [53] Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*. 1990;**28**(10):1021-1034
- [54] Miyoshi N, Kazui H, Ogino A, Ishikawa M, Miyake H, Tokunaga H, Ikejiri Y, Takeda M. Association between cognitive impairment and gait disturbance in patients with idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders*. 2005;**20**(2-3):71-76. DOI: 10.1159/000085858
- [55] Larsson A, Arlig A, Bergh AC, Bilting M, Jacobsson L, Stephensen H, Wikkelsö C, Quantitative SPECT. Cisternography in normal pressure hydrocephalus. *Acta Neurologica Scandinavica*. 1994;**90**(3):190-196
- [56] Kristensen B, Malm J, Fagerland M, Hietala SO, Johansson B, Ekstedt J, Karlsson T. Regional cerebral blood flow, white matter abnormalities, and cerebrospinal fluid hydrodynamics in patients with idiopathic adult hydrocephalus syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1996;**60**(3):282-288
- [57] Momjian S, Owler BK, Czosnyka Z, Czosnyka M, Pena A, Pickard JD. Pattern of white matter regional cerebral blood flow and autoregulation in normal pressure hydrocephalus. *Brain*. 2004;**127**(Pt 5):965-972. DOI: 10.1093/brain/awh131
- [58] Krauss JK, Regel JP, Vach W, Orszagh M, Jüngling FD, Bohus M, Droste DW. White matter lesions in patients with idiopathic normal pressure hydrocephalus and in an age-matched control group: A comparative study. *Neurosurgery*. 1997;**40**(3):491-495
- [59] Ishii K, Kawaguchi T, Shimada K, Ohkawa S, Miyamoto N, Kanda T, Uemura T, Yoshikawa T, Mori E. Voxel-based analysis of gray matter and CSF space in idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders*. 2008;**25**(4):329-335. DOI: 10.1159/000119521
- [60] Sasaki H, Ishii K, Kono AK, Miyamoto N, Fukuda T, Shimada K, Ohkawa S, Kawaguchi T, Mori E. Cerebral perfusion pattern of idiopathic normal pressure hydrocephalus studied by SPECT and statistical brain mapping. *Annals of Nuclear Medicine*. 2007;**21**(1):39-45
- [61] Takaya M, Kazui H, Tokunaga H, Yoshida T, Kito Y, Wada T, Nomura K, Shimosegawa E, Hatazawa J, Takeda M. Global cerebral hypoperfusion in preclinical stage of idiopathic normal pressure hydrocephalus. *Journal of the Neurological Sciences*. 2010;**298**(1-2):35-41. DOI: 10.1016/j.jns.2010.09.001
- [62] Raftopoulos C, Deleval J, Chaskis C, Leonard A, Cantraine F, Desmyttere F, Clarysse S, Brotchi J. Cognitive recovery in idiopathic normal pressure hydrocephalus: A prospective study. *Neurosurgery*. 1994;**35**(3):397-404
- [63] Walchenbach R, Geiger E, Thomeer R, Vanneste J. The value of temporary external lumbar CSF drainage in predicting the outcome of shunting on normal pressure hydrocephalus. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2002;**72**(4):503-506. DOI: 10.1136/jnnp.72.4.503

- [64] Saito M, Nishio Y, Kanno S, Uchiyama M, Hayashi A, Takagi M, Kikuchi H, Yamasaki H, Shimomura T, Iizuka O, Mori E. Cognitive profile of idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders Extra*. 2011;**1**(1):202-211. DOI: 10.1159/000328924
- [65] Bugalho P, Alves L, Miguel R, Ribeiro O. Profile of cognitive dysfunction and relation with gait disturbance in normal pressure hydrocephalus. *Clinical Neurology and Neurosurgery*. 2014;**118**:83-88. DOI: 10.1016/j.clineuro.2014.01.006
- [66] Devito EE, Pickard JD, Salmond CH, Iddon JL, Loveday C, Sahakian BJ. The neuropsychology of normal pressure hydrocephalus (NPH). *British Journal of Neurosurgery*. 2005;**19**(3):217-224. DOI: 10.1080/02688690500201838
- [67] Missori P, Currà A. Progressive cognitive impairment evolving to dementia parallels parieto-occipital and temporal enlargement in idiopathic chronic hydrocephalus: A retrospective cohort study. *Frontiers in Neurology*. 2015;**24**:6-15. DOI: 10.3389/fneur.2015.00015
- [68] Klinge P, Marmarou A, Bergsneider M, Relkin N, Black PM. Outcome of shunting in idiopathic normal-pressure hydrocephalus and the value of outcome assessment in shunted patients. *Neurosurgery*. 2005;**57**(3 Suppl):S40-S52
- [69] Andrén K, Wikkelsø C, Tisell M, Hellström P. Natural course of idiopathic normal pressure hydrocephalus. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2014;**85**:806-180. DOI: 10.1136/jnnp-2013-306117
- [70] Thomas G, McGirt MJ, Woodworth G, Heidler J, Rigamonti D, Hillis AE, Williams MA. Baseline neuropsychological profile and cognitive response to cerebrospinal fluid shunting for idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders*. 2005;**20**(2-3):163-168. DOI: 10.1159/000087092
- [71] Mataró M, Matarín M, Poca MA, Pueyo R, Sahuquillo J, Barrios M, Junqué C. Functional and magnetic resonance imaging correlates of corpus callosum in normal pressure hydrocephalus before and after shunting. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2007;**78**(4):395-398. DOI: 10.1136/jnnp.2006.096164
- [72] Hellström P, Edsbacke M, Blomsterwall E, Archer T, Tisell M, Tullberg M, Wikkelsø C. Neuropsychological effects of shunt treatment in idiopathic normal pressure hydrocephalus. *Neurosurgery*. 2008;**63**(3):527-535. DOI: 10.1227/01.NEU.0000325258.16934.BB
- [73] Koivisto AM, Alafuzoff I, Savolainen S, Sutela A, Rummukainen J, Kurki M, Jääskeläinen JE, Soininen H, Rinne J, Leinonen V, Registry KNPH. Poor cognitive outcome in shunt-responsive idiopathic normal pressure hydrocephalus. *Neurosurgery*. 2013;**72**(1):1-8. DOI: 10.1227/NEU.0b013e31827414b3
- [74] Gözl L, Ruppert FH, Meier U, Lemcke J. Outcome of modern shunt therapy in patients with idiopathic normal pressure hydrocephalus 6 years postoperatively. *Journal of Neurosurgery*. 2014;**121**(4):771-775. DOI: 10.3171/2014.6.JNS131211
- [75] Golomb J, Wisoff J, Miller DC, Boksay I, Kluger A, Weiner H, Salton J, Graves W. Alzheimer's disease comorbidity in normal pressure hydrocephalus: Prevalence and shunt response. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2000;**68**(6):778-781

- [76] Savolainen S, Paljärvi L, Vapalahti M. Prevalence of Alzheimer's disease in patients investigated for presumed normal pressure hydrocephalus: A clinical and neuropathological study. *Acta Neurochirurgica*. 1999;**141**(8):849-853
- [77] Pyykkö OT, Lumela M, Rummukainen J, Nerg O, Seppälä TT, Herukka SK, Koivisto AM, Alafuzoff I, Puli L, Savolainen S, Soininen H, Jääskeläinen JE, Hiltunen M, Zetterberg H, Leinonen V. Cerebrospinal fluid biomarker and brain biopsy findings in idiopathic normal pressure hydrocephalus. *PLoS One*. 2014;**9**(3):e91974. DOI: 10.1371/journal.pone.0091974
- [78] Yasar S, Jusue-Torres I, Lu J, Robison J, Patel MA, Crain B, Carson KA, Hoffberger J, Batra S, Sankey E, Moghekar A, Rigamonti D. Alzheimer's disease pathology and shunt surgery outcome in normal pressure hydrocephalus. *PLoS One*. 2017;**12**(8):e0182288. DOI: 10.1371/journal.pone.0182288
- [79] Kazui H, Mori E, Hashimoto M, Ishikawa M, Hirono N, Takeda M. Effect of shunt operation on idiopathic normal pressure hydrocephalus patients in reducing caregiver burden: Evidence from SINPHONI. *Dementia and Geriatric Cognitive Disorders*. 2011;**31**(5):363-370. DOI: 10.1159/000328625
- [80] Petersen J, Hellström P, Wikkelsø C, Lundgren-Nilsson A. Improvement in social function and health-related quality of life after shunt surgery for idiopathic normal-pressure hydrocephalus. *Journal of Neurosurgery*. 2014;**121**(4):776-784. DOI: 10.3171/2014.6.JNS132003
- [81] Calcagni ML, Lavallo M, Mangiola A, Indovina L, Leccisotti L, De Bonis P, Marra C, Pelliccioni A, Anile C, Giordano A. Early evaluation of cerebral metabolic rate of glucose (CMRglu) with 18-F-FDG PET/CT and clinical assessment in idiopathic normal pressure hydrocephalus (INPH) patients before and after ventricular shunt placement: Preliminary experience. *European Journal of Nuclear Medicine and Molecular Imaging*. 2012;**39**(2):236-241. DOI: 10.1007/s00259-011-1950-6
- [82] Calcagni ML, Taralli S, Mangiola A, Indovina L, Lavallo M, De Bonis P, Anile C, Giordano A. Regional cerebral metabolic rate of glucose evaluation and clinical assessment in patients with idiopathic normal pressure hydrocephalus before and after ventricular shunt placement. A prospective analysis. *Clinical Nuclear Medicine*. 2013;**38**(6):426-431. DOI: 10.1097/RLU.0b013e31828e949b
- [83] Dumarey NE, Massager N, Laureys S, Goldman S. Voxel-based assessment of spinal tap test-induced regional cerebral blood flow changes in normal pressure hydrocephalus. *Nuclear Medicine Communications*. 2005;**26**(9):757-763
- [84] Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, Vogel JW, Kramer JH, van der Vlies AE, La Joie R, Rosen HJ, van der Flier WM, Grinberg LT, Rozemuller AJ, Huang EJ, van Berckel BN, Miller BL, Barkhof F, Jagust WJ, Scheltens P, Seeley WW, Rabinovici GD. The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. *Brain* 2015;**138**(Pt 9):2732-2749. DOI: 10.1093/brain/awv191

- [85] Hamilton R, Patel S, Lee EB, Jackson EM, Lopinto J, Arnold SE, Clark CM, Basil A, Shaw LM, Xie SX, Grady MS, Trojanowski JQ. Lack of shunt response in suspected idiopathic normal pressure hydrocephalus with Alzheimer disease pathology. *Annals of Neurology*. 2010;**68**(4):535-540. DOI: 10.1002/ana.22015
- [86] Leinonen V, Koivisto AM, Alafuzoff I, Pyykkö OT, Rummukainen J, von Und Zu, Fraunberg M, Jääskeläinen JE, Soininen H, Rinne J, Savolainen S. Cortical brain biopsy in long-term prognostication of 468 patients with possible normal pressure hydrocephalus. *Neurodegenerative Diseases*. 2012;**10**(1-4):166-169. DOI: 10.1159/000335155
- [87] Jack CR Jr, Wiste HJ, Weigand SD, Rocca WA, Knopman DS, Mielke MM, Lowe VJ, Senjem ML, Gunter JL, Preboske GM, Pankratz VS, Vemuri P, Petersen RC. Age-specific population frequencies of cerebral b-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: A cross-sectional study. *Lancet Neurology* 2014;**13**(10):997-1005. DOI: 10.1016/S1474-4422(14)70194-2
- [88] Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Stephen Salloway S, Van der Flieret WM. Alzheimer's disease. *Lancet* 2016;**388**:505-517
- [89] Kapaki EN, Paraskevas GP, Tzerakis NG, Sfagos C, Seretis A, Kararizou E, Vassilopoulos D. Cerebrospinal fluid tau, phospho-tau181 and beta-amyloid1-42 in idiopathic normal pressure hydrocephalus: A discrimination from Alzheimer's disease. *European Journal of Neurology*. 2007;**14**(2):168-173. DOI: 10.1111/j.1468-1331.2006.01593.x
- [90] Agren-Wilsson A, Lekman A, Sjöberg W, Rosengren L, Blennow K, Bergenheim AT, Malm J. CSF biomarkers in the evaluation of idiopathic normal pressure hydrocephalus. *Acta Neurologica Scandinavica*. 2007;**116**(5):333-339. DOI: 10.1111/j.1600-0404.2007.00890.x
- [91] Jeppsson A, Zetterberg H, Blennow K, Wikkelsø C. Idiopathic normal-pressure hydrocephalus: Pathophysiology and diagnosis by CSF biomarkers. *Neurology*. 2013;**80**(15):1385-1392. DOI: 10.1212/WNL.0b013e31828c2fda
- [92] Kang K, Ko PW, Jin M, Suk K, Lee HW. Idiopathic normal-pressure hydrocephalus, cerebrospinal fluid biomarkers, and the cerebrospinal fluid tap test. *Journal of Clinical Neuroscience*. 2014;**21**(8):1398-1403. DOI: 10.1016/j.jocn.2013.11.039
- [93] Jingami N, Asada-Utsugi M, Uemura K, Noto R, Takahashi M, Ozaki A, Kihara T, Kageyama T, Takahashi R, Shimohama S, Kinoshita A. Idiopathic normal pressure hydrocephalus has a different cerebrospinal fluid biomarker profile from Alzheimer's disease. *Journal of Alzheimer's Disease*. 2015;**45**(1):109-115. DOI: 10.3233/JAD-142622
- [94] Chen Z, Liu C, Zhang J, Relkin N, Xing Y, Li Y. Cerebrospinal fluid A β 42, t-tau, and p-tau levels in the differential diagnosis of idiopathic normal-pressure hydrocephalus: A systematic review and meta-analysis. *Fluids Barriers CNS*. 2017;**14**:13. DOI: 10.1186/s12987-017-0062-5
- [95] Graff-Radford NR. Alzheimer CSF biomarkers may be misleading in normal-pressure hydrocephalus. *Neurology*. 2014;**83**(17):1573-1575. DOI: 10.1212/WNL.0000000000000916

- [96] Picascia M, Zangaglia R, Bernini S, Minafra B, Sinforiani E, Pacchetti CA. Review of cognitive impairment and differential diagnosis in idiopathic normal pressure hydrocephalus. *Functional Neurology*. 2015;**30**(4):217-228
- [97] Picascia M, Minafra B, Zangaglia R, Gracardi L, Pozzi NG, Sinforiani E, Pacchetti C. *spectrum* Of cognitive disorders in idiopathic normal pressure hydrocephalus. *Functional Neurology* 2016;**31**(3):143-147
- [98] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N; Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society UPDRS revision task force Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*. 2008;**23**(15):2129-2170. DOI: 10.1002/mds.22340
- [99] Antonini A, Abbruzzese G, Ferini-Strambi L, Tilley B, Huang J, Stebbins GT, Goetz CG, Barone P, MDS-UPDRS Italian Validation Study Group, Bandettini di Poggio M, Fabbrini G, Di Stasio F, Tinazzi M, Bovi T, Ramat S, Meoni S, Pezzoli G, Canesi M, Martinelli P, Maria Scaglione CL, Rossi A, Tambasco N, Santangelo G, Picillo M, Morgante L, Morgante F, Quatrone R, Sensi M, Pilleri M, Biundo R, Nordera G, Caria A, Pacchetti C, Zangaglia R, Lopiano L, Zibetti M, Zappia M, Nicoletti A, Quattrone A, Salsone M, Cossu G, Murgia D, Albanese A, Del Sorbo F. MDS-UPDRS Italian validation study group. Validation of the Italian version of the Movement Disorder Society-unified Parkinson's disease rating scale. *Neurological Sciences*. 2013;**34**(5):683-687. DOI: 10.1007/s10072-012-1112-z
- [100] Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*. 2002;**8**(3):448-460