

A review of cognitive impairment and differential diagnosis in idiopathic normal pressure hydrocephalus

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Summary

Idiopathic normal pressure hydrocephalus (iNPH) is a complex and still underestimated pathology. In the early stages, the cognitive profile is characterized mainly by impairments of attention, psychomotor speed and memory, suggesting frontal involvement; patients with more advanced iNPH show overall cognitive deterioration. The memory impairment, however, seems to be milder than that seen in Alzheimer's disease (AD). Clinical and neuroimaging data are crucial for the diagnosis of iNPH, but the presence of different variables, such as comorbidities, and the possible overlapping with other neurodegenerative diseases, AD in particular, make the differential diagnosis difficult. To date studies seeking to identify possible biological markers have provided inconclusive results; moreover reliable indices predictive of a good response to surgery are still lacking. There is a need for further studies with longer follow-ups and for closer interaction among the different professionals involved.

KEY WORDS: Alzheimer's disease, biological markers, cognitive impairment, idiopathic normal pressure hydrocephalus, shunt surgery

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) was first described in 1965 by Hakim and Adam as ventric-

ular dilation accompanied by a progressive triad of a gait disturbance, "dementia" and incontinence. Gait and balance disorders are the leading presentations, whereas cognitive decline and incontinence appear as the disease progresses (Williams and Relkin, 2013). The incidence of iNPH is between 2 and 6% among people affected by any dementia condition; it is considered an infrequent disease, but its occurrence is probably underestimated. Brean and Eide (2008) 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. In a more recent epidemiological study (Jaraj et al., 2014), the prevalence of probable iNPH was 0.2% in subjects aged 70-79 years and 5.9% in those aged 80 years and older, with no difference between men and women. Moreover, the authors underlined that "the number of subjects with iNPH is probably much higher than the number of persons currently treated", and that the prevalence increases with increasing age. A high incidence was also reported by Iseki et al. (2014) in a 10-year follow-up study of a population of 70 year olds from a rural Japanese community. A recent systematic epidemiological review (Martin-Láez et al., 2015) confirmed that this pathology is under-diagnosed. Interest in this condition is due to the fact that it can be considered a potentially reversible dementia; in fact, cerebrospinal fluid (CSF) shunt surgery has been reported to improve the symptoms (Adams et al., 1965). The first guidelines and operating criteria for the diagnosis and management of the condition were proposed in 2005 by the Japanese Society of Normal Pressure Hydrocephalus but were available only in Japanese; in the same year, Marmarou et al. (2005) published English language guidelines designed to be "acceptable in the United States and abroad". Then, in 2008, Ishikawa et al. proposed an English version of the previous Japanese guidelines in order to make them known worldwide (Ishikawa et al., 2008). 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. (2012) published a revision of the English language version of the Japanese guidelines. More recently, Williams and Relkin (2013) have published detailed indications on the diagnosis and management of iNPH, stressing the concept that the starting point should be a comprehensive history and neurological examination, review of neuroimaging studies, and evaluation of the differential diagnosis.

However, even though research in this field has advanced, iNPH must still be considered a complex pathology whose diagnosis and management continue to present many problems. Here we present a review of this topic focusing on three main aspects of iNPH: i) the characteristics of the cognitive impairment, ii) the differential diagnosis with Alzheimer's disease (AD), iii) changes in cognition after shunt surgery. To our knowledge, there has been no previous literature review of this topic; our analysis is intended to better specify the cognitive characteristics of iNPH and examine the related diagnostic issues.

Methods

In order to address all three aspects, we conducted a literature search in the PubMed database. Studies from 1991 to 2015 were included in the search and we used the following search terms: idiopathic normal pressure hydrocephalus, cognitive impairment, Alzheimer's disease, biological markers, shunt surgery. Articles were considered only if they concerned clinical studies and reported data on formal neuropsychological evaluations. Studies in languages other than English were excluded.

Cognitive impairment in idiopathic normal pressure hydrocephalus

The cognitive and behavioral disturbances accompanying iNPH have been commonly described as "fronto-subcortical dementia" (Ogino et al., 2006; Tarnaris et al., 2011). This clinical term is used to refer to a pattern of mental decline, characterized by executive dysfunction, psychomotor slowing and mood symptoms, especially apathy (Larsson et al., 1991; Mega and Cummings, 1994), that is often present in patients with iNPH. Boon et al. (1997), in a study that 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. (1999), on the basis of a Mini-Mental State Examination (MMSE) score cut-off, divided their sample of 11 patients into two groups: demented and non-demented. They then evaluated different cognitive functions through neuropsychological measures; the results suggested that there exist two cognitive profiles in iNPH, one observed in patients at a less advanced disease stage, who present isolated frontal lobe dysfunction, and the other observed in those who have reached a more advanced stage and present severe global cognitive dysfunction. The non-demented iNPH patients failed on attentional tasks which may reflect a deficit in cognitive flexibility, similar to patients with frontal lobe excision and patients with fronto-subcortical dementia such as Parkinson's disease (Owen et al., 1991, 1992), and unlike patients with AD in which frontal functions are spared (Owen et al., 1990). Ogino et al. (2006), in a well-controlled study, ana-

lyzed 21 patients with iNPH and 42 patients with AD, using a neuropsychological assessment investigating different cognitive domains. They observed that patients with iNPH had more severe impairment of attention, psychomotor speed and calculation than those with AD, while memory function and orientation were more preserved. Miyoshi et al. (2005) 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. The results indicated that frontal lobe functions were impaired in patients with iNPH.

Tarnaris et al. (2011), analyzing cognitive performances of 10 patients with iNPH through a complete neuropsychological assessment (language, memory, executive functions, visuospatial abilities, attention), confirmed that all the patients had subcortical cognitive impairment, characterized in particular by dysexecutive dysfunction and slowed mental processing.

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 (Larsson et al., 1994; Kristensen et al., 1996; Momjian et al., 2004). Thus, the cognitive impairment in iNPH could be attributed to accentuated damage in the frontal lobe. On the basis of the finding that periventricular white matter cerebral blood flow was reduced in iNPH (Momjian et al., 2004) 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 (Krauss et al., 1997; Iddon et al., 1999; Momjian et al., 2004). 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 (Ogino et al., 2006). However, a neuroimaging study (Ishii et al., 2008) 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 (Sasaki et al., 2007; Takaya et al., 2010).

Even though the cognitive decline in iNPH is often subsumed under the heading of fronto-subcortical dementia, this definition is probably reductive given that patients with iNPH can be impaired in broader cognitive domains. Indeed, the cognitive deficits observed in iNPH extend beyond executive function, attention, working memory and episodic memory to visuo-perceptual and visuospatial functions (Raftopoulos et al., 1994; Kristensen et al., 1996; Boon et al., 1997; Walchenbach et al., 2002). Saito et al. (2011), in a well-controlled study of 32 iNPH patients, 32 AD patients and 30 healthy elderly controls, used an extensive and comprehensive neuropsychological battery to investigate, exhaustively, all the different cognitive domains: language, memory, executive functions, visuospatial and visuo-perceptual abilities, attention, mental processing speed. Their results suggested that iNPH is associated with impairments in various aspects of cognition involving both

frontal-executive and posterior-cortical functions, such as visuo-perceptual and visuo-spatial abilities. In particular, defective performances were found on the visual discrimination and visual counting tasks. Bugalho et al. (2014) compared 17 iNPH patients with 14 healthy controls and observed that visuo-spatial 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. Walchenbach et al. (2002) analyzed 51 iNPH patients, administering the MMSE and a series of neuropsychological tests assessing both cortical functions (language, visuo-perceptual skills and praxis, 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. (2006) 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. Saito et al. (2011) found that both recognition and recall were impaired in a similar fashion in iNPH and AD groups, suggesting that memory impairment in iNPH is not exclusively ascribable to frontal lobe dysfunction.

Quoting Devito et al. (2005), we can conclude that the features of cognitive decline in iNPH patients can be varied: "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 it. Devito et al. (2005) proposed a clinical assessment protocol for iNPH in which importance was attached to the evaluation of cognitive and emotional domains. Ogino et al. (2006) 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. (2011) 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 visuo-perceptual and visuo-spatial functions. Bugalho et al. (2014) employed a cognitive assessment protocol focused on various cognitive domains (global cognitive function, verbal memory, impulse control, verbal fluency, working memory, attention, visuo-spatial reasoning, visuo-constructive abilities) and also on mood and hand dexterity. In a recent study by Missori and Currà (2015), all the patients

underwent the following 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 the diagnostic differentiation of iNPH from other diseases, in particular AD, can present some difficulties, a detailed characterization of cognitive dysfunction in iNPH is needed. The MMSE is a useful instrument for an initial screening, but it cannot be the only cognitive assessment used as it is not able to detect specific cognitive profiles, frontal dysfunction in particular. Therefore, the neuropsychological assessment has to include sensitive and exhaustive measures investigating all the different cognitive domains.

Table I summarizes the characteristics of the studies reported.

Idiopathic normal pressure hydrocephalus and Alzheimer's disease

As reported above, iNPH has to be differentiated from other neurodegenerative diseases variously characterized by gait disturbances and cognitive impairment, namely AD, 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. The differentiation from AD is particularly important. As for cognitive impairment, as explained in the previous section, impairment of frontal lobe-related functions is not frequent in AD, at least in the early stages; 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; from this perspective, many studies have tried to identify biological markers both for improving the diagnosis and predicting shunt efficacy. Savolainen et al. (1999) performed cortical biopsy in 118 of 223 iNPH patients; normal brain tissue was found in 66 subjects, 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 finding of positive biopsies for neuritic plaques was also reported by Golomb et al. (2000); 81/117 patients with possible iNPH underwent a structured psychiatric interview; of these 81 patients, 77 were cognitively impaired, recording a Global Deterioration Scale (GDS) score ≥ 3 ; of these 77 patients, 56 had a cortical biopsy. Neuritic plaques were found in 23 patients; the subjects with positive biopsies were more cognitively impaired (higher GDS and lower MMSE scores) as well as more gait impaired than the patients with negative biopsies. The prevalence of neuritic plaques increased in parallel with

dementia severity from 18% in patients with GDS ≥ 3 to 75% in those with GDS scores ≥ 6 . However, in this sample, concomitant Alzheimer pathology did not strongly influence the clinical response to shunt surgery, irrespective of its severity. On the contrary, Hamilton et al. (2010) found the degree of Alzheimer pathology to be

important in predicting the response to surgery. They studied 37 patients: biopsy was negative in 12 patients, whereas 25 subjects showed a high percentage (above 60%) not only of neuritic plaques but also of neurofibrillary tangles. Patients with moderate-to-severe tau and beta-amyloid (A β) pathology showed more severe base-

Table 1 - Cognitive impairment in idiopathic normal pressure hydrocephalus.

AUTHORS	SAMPLE	METHODS	RESULTS
Boon et al., 1997	101 iNPH patients (mean age: 73.7 y) 10 healthy controls (mean age: 72.4 y)	Neuropsychological evaluation: MMSE; memory (10 Word Memory Test, Digit Span); psychomotor speed and attention (Finger tapping, TMT A)	Severe impairment of attention and psychomotor speed.
Iddon et al., 1999	11 iNPH patients Group 1: 5 demented (mean age: 70.2 y) Group 2: 6 non-demented (mean age: 69.2 y)	Neuropsychological evaluation: Group 1: MMSE; memory (KOLT). Group 2: MMSE; KOLT; verbal fluency and memory, attention task from CANTAB.	Early stages of iNPH were characterized by frontal pattern of mental impairment, but if the pressure was not relieved quickly, a severe global cognitive dysfunction could develop.
Walchenbac et al., 2002	51 iNPH patients (mean age: 77 y)	Neuropsychological evaluation: MMSE; memory (10 Word Memory Test); frontal functions, mental processing speed, concept shifting, attention (TMT A and B, Stroop Test, Symbol Digit Memory Test).	The cognitive deficit was global; memory deficit was of the frontal lobe type, in which recall is disproportionately affected with respect to recognition. A clinical improvement was seen after 2 months in 73% of the patients.
Miyoshi et al., 2005	17 iNPH patients (mean age: 74.8 y) 17 AD patients (mean age: 74.3 y)	Neuropsychological evaluation: some subtests of the MMSE; frontal lobe functions (FAB, verbal fluency)	Frontal lobe functions were impaired.
Ogino et al., 2006	21 iNPH (mean age: 74.5 y) 42 AD patients (mean age: 74.4 y)	Neuropsychological evaluation: MMSE; ADAS, WMS-R and WAIS-R	iNPH patients had more severe impairment of attention, psychomotor speed and calculation than AD patients. Memory function and orientation were more preserved in iNPH than in AD patients.
Saito et al., 2011	32 iNPH patients (mean age: 76.3 y) 32 AD patients (mean age: 76.0 y) 30 healthy elderly controls (mean age: 76.8 y)	Neuropsychological evaluation: MMSE; memory (Digit Span, Spatial Span, Word recall and Word recognition subtests of ADAS); attention (TMT A); FAB; language (Object naming, Word fluency); visuospatial functions (Visual discrimination, Overlapping figures and Visual counting tasks)	Patients with iNPH were impaired in various aspects of cognition involving both frontal-executive functions and posterior cortical functions.
Tarnaris et al., 2011	10 iNPH patients (mean age: 71.4 y)	Neuropsychological evaluation: test of premorbid and current intelligence (NART-R and WAIS-R); verbal and visual recognition, recognition memory (RMT-Words and RMT-Faces); executive functions and speed of information processing (phonemic verbal fluency and TMT B, Cancelling 0s or TMT A).	All the patients had subcortical cognitive impairment, characterized by slowed mental processing.

continued

Table 1 - (cont.)

AUTHORS	SAMPLE	METHODS	RESULTS
Bugalho et al., 2014	17 iNPH patients (mean age: 76.5 y) 14 healthy controls (mean age: 75.1 y)	Neuropsychological evaluation: MMSE; memory (WMS-R); attention and working memory (Stroop Test, Digit span, Letter cancelling); visuospatial reasoning (Raven's Colored Matrices); visuoconstructive ability and visuospatial memory (Rey Complex Figure-copy and delayed recall); hand dexterity (Purdue Pegboard Test).	Patients presented widespread cognitive dysfunction with a predominance of visuospatial deficits.
Missori and Currà, 2015	21 iNPH patients (mean age: 65.3 y)	Neuropsychological evaluation: MMSE; verbal memory (Rey's 15 words immediate and delayed recall, Digit span); frontal and executive functions (FAB, WCST, Analogies test; TMT, Attentive Matrices).	Progression of cognitive impairment (only MMSE scores were considered for the analysis) in parallel with ventricular parieto-occipital and temporal horn enlargement.

Abbreviations: iNPH=idiopathic normal pressure hydrocephalus; AD=Alzheimer's disease; TMT A/B=Trail Making Test part A/B; MMSE=Mini-Mental State Examination; KOLT=Kendrick Object Learning Test; CANTAB=Cambridge Neuropsychological Test Automated Battery; FAB=Frontal Assessment Battery; ADAS=Alzheimer's Disease Assessment Scale; WMS-R=Wechsler Memory Scale-Revised; WAIS-R=Wechsler Adult Intelligence Scale-Revised; NART-R=National Adult Reading Test-Revised; RMT-Words=Recognition Memory Test-Words; RMT-Face=Recognition Memory Test-Faces; WMS=Wechsler Memory Scale; WCST=Wisconsin Card Sorting Test.

line cognitive impairment and poorer performance post-operatively on NPH symptom severity scales and measures of cognition, while patients with mild Alzheimer pathology responded well to shunting, thus suggesting that some patients are relatively unimpaired by the presence of cortical Alzheimer pathology. The authors suggested that the differences in their results compared with those of previous studies could be explained by the different methods employed. The predictive value of brain biopsy for the long-term outcome of iNPH was evaluated by Leinonen et al. (2012) in 468 patients with possible iNPH; the presence of A β was detected in 197 (42%) patients, and together with tau pathology in 44 cases (9%), but it did not affect survival.

On the other hand, neuritic plaques can also be present in the brains of normal healthy individuals (Jack et al., 2014); therefore, in order to improve the differential diagnosis, CSF biological markers have also been investigated. The specific combination of both low CSF A β -42 and elevated CSF phosphorylated tau (P-tau) is in fact considered to be the biological signature of AD, where low A β levels reflect amyloid deposition and high tau levels indicate neuronal damage (Blennow and Hampel, 2003). In 2007 Kapaki et al. studied 85 patients (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 the AD patients; therefore the authors concluded that P-tau may be a useful marker in the differentiation of iNPH from AD. In the same year Agren-Wilsson et al. (2007) studied 62 iNPH patients, 26 patients with subcortical vascular encephalopathy and 23 healthy controls. The CSF concentration of neurofilament light protein (NLP) was elevated in the iNPH and vascular encephalopathy patients compared with the controls, while 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. The authors concluded that the combined pattern of several markers, rather than one specific marker, was able to distinguish iNPH patients from vascular patients and controls. Jeppsson et al. (2013) also reported lower CSF levels of both T-tau and P-tau and amyloid precursor protein (APP) in 28 iNPH patients compared with 20 healthy controls, while NLP was elevated. After surgery there was an increase in most of these markers; these data were interpreted as due to a reduced periventricular metabolism and axonal degeneration rather than to major cortical damage. Kang et al. (2014) found lower CSF A β -42 levels and lower P-tau levels, compared with the control reference value, in 35 iNPH patients; 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. (2015) studied 55 iNPH patients, 20 AD patients, 11 patients with corticobasal syndrome and seven patients with spinocerebellar degeneration. Tau levels were significantly decreased in iNPH versus AD patients, especially in tap test responders; the authors concluded that CSF tau can be considered useful for differentiating iNPH from AD. Pyykkö et al. (2014) performed both cortical biopsy and CSF sampling in a population of 102 patients, subsequently subdivided into 53 with iNPH, 26 with AD and 23 with other diagnoses. In the iNPH group A β load in the brain biopsy showed a negative correlation with CSF levels of A β -42; no differences in markers of neuroinflammation and neuronal damage were found between iNPH and AD patients. No differences in CSF A β levels or tau biomarkers between shunt-responding and non-responding iNPH patients were reported, even though non-responding patients were older.

Therefore the results from the literature are not conclusive. Graff-Radford (2014) conclude that, at present, 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, but rather could result from impaired clearance; the findings of pre-shunt low tau protein levels may have the same explanation. Indeed, in iNPH, since the brain is compressed, the interstitial space is reduced 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 thus allows protein waste fragments to drain into the CSF; increased levels of CSF proteins after shunting have in fact been reported. Graff-Radford observed that this hypothesis does not exclude the reduced periventricular metabolism hypothesis advanced by Jeppsson et al. (2013), and suggests prospective A β PET studies in order to determine whether this technique is able to distinguish iNPH from comorbid AD.

Table II summarizes the characteristics of the studies reported.

Cognitive impairment after shunt surgery

iNPH is considered a potentially reversible dementia and the treatment of choice is ventriculo-peritoneal or atrial shunt device placement. Specific criteria and guidelines have been defined for the surgical procedure and the post-operative and long-term care, including the management of complications (Marmarou et al., 2005; Mori et al., 2012). The true incidence of this procedure is not well defined (Martin-Láez et al., 2015). Many studies describe a global improvement after surgery in a high percentage of patients. 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; it has been suggested that the one-year post-shunt period can be considered a determinant of long-term results of the treatment (Klinge et al., 2005). Shunt surgery can help to reduce cognitive impairment, especially if it is performed during the early stage of deterioration; if the pressure is not relieved quickly by a shunt patients with severe iNPH will in fact develop overall cognitive impairment (Iddon et al., 1999; Mori et al., 2012).

Table II - Idiopathic normal pressure hydrocephalus and Alzheimer's disease.

AUTHORS	SAMPLE	METHODS	RESULTS
Savolainen et al., 1999	223 iNPH patients (mean age: under 75 y)	Cortical biopsy in 118 out of 223 patients	Normal brain tissue in 66 patients; Alzheimer pathology (neuritic plaques) was found in over 40%.
Kapaki et al., 2007	18 iNPH patients (mean age: 69 y), 67 AD patients (mean age: 66 y), 72 healthy controls (mean age:64 y)	CSF sampling: A β -42, T-tau and P-tau levels were measured	A β -42 levels were significantly decreased in both diseases as compared with controls, while P-tau levels were significantly increased only in AD patients
Agren-Wilsson et al., 2007	62 iNPH patients (mean age: 72 y), 26 patients with subcortical vascular encephalopathy (mean age: 73 y), 23 healthy controls (mean age: 73 y)	CSF sampling: NLP, T-tau, P-tau and A β -42 levels were measured	NLP was elevated in iNPH and vascular encephalopathy compared with the controls; 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.
Golomb et al., 2000	117 iNPH patients (mean age 76.3 y)	81/117 received a structured psychiatric interview, 77/81 were cognitively impaired (GDS \geq 3); 56/77 received cortical biopsy	23/56 patients presented neuritic plaques and were more cognitively impaired (higher GDS scores and lower MMSE scores) as well as more gait impaired than patients without plaques. The prevalence of neuritic plaques increased in parallel with dementia severity from 18% for patients with GDS \geq 3 to 75% for patients with GDS scores \geq 6.

continued

Table II - (cont.)

AUTHORS	SAMPLE	METHODS	RESULTS
Hamilton et al., 2010	37 iNPH patients (mean age: 75 y)	Cortical biopsy	Negative biopsy in 12 patients, 25 patients showed positive biopsy (neuritic plaques and neurofibrillary tangles). Patients with moderate-to-severe tau and A β pathology showed more severe baseline cognitive impairment and poorer cognitive and motor performance postoperatively.
Leinonen et al., 2012	468 iNPH patients (mean age: 72.1 y)	Cortical biopsy	197 patients (42%) presented A β , 44 (9%) both A β and hyper-phosphorylated tau; no effects on survival.
Jeppsson et al., 2013	28 iNPH patients (mean age: 69 y) 20 healthy controls (mean age: 70 y)	CSF sampling: NLP, T-tau and P-tau, APP, neuroinflammatory markers	NLP was elevated, T-tau, P-tau and APP were lower in iNPH than in controls; increase after surgery
Kang et al., 2014	35 iNPH patients (mean age: 72.7 y)	CSF sampling: A β -42 and P-tau levels were measured	CSF A β and P-tau levels were lower in iNPH versus control reference value; 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.
Pyykko et al., 2014	102 patients subsequently subdivided into: 53 iNPH patients (mean age: 75.5 y), 26 AD patients (mean age: 78.3 y), 23 with other diagnoses (mean age: 70.6 y)	Cortical biopsy and CSF sampling; A β -42, T-tau and P-tau levels, pro-inflammatory markers and biomarkers of neuronal damage were measured	A β load in the brain biopsy showed a negative correlation with CSF levels of A β -42; no differences in markers of neuroinflammation and neuronal damage between iNPH and AD patients. No differences in CSF A β levels or tau biomarkers between shunt-responding and non-responding iNPH patients.
Jingami et al., 2015	55 iNPH patients (mean age: 76.5 y), 20 AD patients (mean age: 71.8 y), 11 patients with CBS (mean age: 71.7 y), 7 patients with SCD (mean age: 70.4 y)	CSF sampling: A β -42, T-tau and P-tau levels were measured	Tau levels were significantly decreased in iNPH with respect to AD especially in tap test responder patients.

Abbreviations: iNPH= idiopathic normal pressure hydrocephalus; AD=Alzheimer's disease; CBS=corticobasal syndrome; SCD=spinocerebellar degeneration; GDS=Global Deterioration Scale; APP=amyloid precursor protein; CSF=cerebrospinal fluid; MMSE=Mini-Mental State Examination; A β =amyloid beta; NLP=neurofilament light protein; P-tau=phosphorylated tau; T-tau=total tau.

There is no general agreement about which cognitive functions are more likely to be restored after shunt placement. Iddon et al. (1999), 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 non-demented patients the frontal deficits remained unchanged. As reported by Thomas et al. (2005), ver-

bal 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 three months after surgery showed an overall cognitive improvement (defined as a 4-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. Memory, frontal lobe and visuoconstructive functions can also show improvements at six months (Mataró et al., 2007) and one year (Raftopoulos et al., 1994) after shunt surgery. Mataró et al. (2007) also reported a significant increase in the global corpus callosum size on MRI. In a series of 47 consecutive patients reported by Hellström et al. (2008), most of the wide range of cognitive functions typically affected in iNPH were found to be improved at three months after shunt placement; the more severe functional deficits showed the greatest improvements, although they were not completely restored to the levels recorded in healthy controls. Saito et al. (2011) found that frontal functions (assessed using the TMT and FAB) were improved at one year after the shunt procedure in 26 out of 32 patients; in this paper the authors raised the important question of the possible practice effect when patients are evaluated after a short interval of time. Koivisto et al. (2013), 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 presented dementia without any other signs of neurodegenerative or vascular diseases; at baseline these subjects had the full triad of symptoms. Götz et al. (2014) followed up 147 patients for six 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. 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. Golomb et al. (2000), 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. (2002), 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 five 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. Cortical biopsies were also performed; the patients with a positive biopsy had worsened more than those with a negative biopsy after one year, but mortality was not increased in these patients. On the contrary, as reported in the previous section, Pyykko et al. (2014) 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 formal neuropsychological evaluation was performed in order to better define the response to shunt placement. Some studies have focused on the caregiver. A decrease in caregiver burden was reported by Kazui et al. (2011) in the caregivers of 81 iNPH patients one 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. (2014) evaluated the impact of shunt surgery on 37 patients six months after the procedures; 24 (65%) showed a clinical improvement, while in 31 (86%) quality of life returned almost within normal range as a consequence of their greater independence. These authors also investigated the impact of the surgery on caregiver burden, and found this to be 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. (2012) performed F-FDG PET/CT scanning three days before and one week after shunt placement. 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 three out of 19 subjects. These results were confirmed in a further study by the same authors (Calcagni et al., 2013). In an earlier study, Dumarey et al. (2005) 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. The rapid occurrence of functional changes, in the absence (at least in the early stages) of morphological ones, seems 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.

Table III summarizes the characteristics of the studies reported.

Table III - Cognitive impairment after shunt surgery.

AUTHORS	SAMPLE	METHODS	RESULTS
Raftopoulos et al., 1994	23 iNPH patients (mean age: 70 y)	Follow-up after two months and one year. Neuropsychological evaluation: memory (Buschke-Fuld test, Wechsler Digit Span, Rey-Osterrieth Complex Figure Test-delayed recall); visuoconstructive functions (Rey-Osterrieth Complex Figure Test-copy), visuospatial reasoning (Raven's Colored Progressive Matrices); language (Boston Diagnostic Aphasia Examination).	Improvement of memory, frontal lobe and visuoconstructive functions in 66.6% of the patients, the greatest improvement was recorded at 2 months postoperatively, except for the visuoconstructive skills, which improved between 2 months and 1 year.
Iddon et al., 1991	11 iNPH patients Group 1: 5 demented (mean age: 70.2 y) Group 2: 6 non-demented (mean age: 69.2 y)	Follow-up six months after shunt. Neuropsychological evaluation: Group 1: MMSE; memory (KOLT). Group 2: MMSE; KOLT; verbal fluency and memory, attention task from the CANTAB battery.	Demented patients showed a significant improvement; in non-demented patients the frontal deficits remained unchanged.
Golomb et al., 2000	56 iNPH patients (mean age 76.1 y)	Mean follow-up: 4.3 months Neuropsychological evaluation: MMSE; Guild paragraph recall test; attention and speed processing (Digit Symbol Substitution Test, TMT A/B, Mefferd and Moran perceptual speed test, Purdue Pegboard Test).	Small but significant improvements on attention and perceptual speed tests in patients with a negative biopsy.
Savolainen et al., 2002	51 iNPH patients, 25 underwent shunt (mean age: 66.6 y)	Follow-up after one year and after five years. Neuropsychological evaluation: MMSE; current intelligence (WAIS-R); memory (immediate and delayed wordlist, recognition of words, visual WMS-R); attention (TMT A/B, Stroop Test); psychomotor speed (tapping test)	One year after surgery, 72% of patients presented a good improvement in activities of daily living, 58% in urinary incontinence and 57% walked better; after five years the positive effects of shunt remained.
Thomas et al., 2005	42 iNPH patients (mean age: 69.1 y)	Follow-up at least three months after shunt. Neuropsychological evaluation: MMSE; memory, visuoconstructive and psychomotor speed tests.	22 (53.2%) showed an overall cognitive improvement (4-point improvement on MMSE) and significant improvements in verbal memory and psychomotor speed. Impairment of both verbal memory and visuoconstructive functions at baseline may predict response to shunt.
Mataró et al., 2007	14 out 18 iNPH patients (mean age: 74.6 y)	Follow-up after six months. Neuropsychological evaluation: MMSE; attention and memory (Digit Span, AVLT, Visual retention); frontal functions (fluency, TMT A/B, Stroop Test); psychomotor speed (Purdue Pegboard Test)	Improvements in memory, frontal lobe and visuoconstructive functions; significant increase in global corpus callosum size on MRI.
Hellström et al., 2008	47 iNPH patients (mean age: 73 y) 159 healthy controls (mean age: 73 y)	Follow-up after three months. Neuropsychological evaluation: memory (Digit Span, Rey AVLT); attention and psychomotor speed (Simple Reaction Time, Target Reaction Time, Grooved Pegboard, Tracks Task, Swedish Stroop Test)	Improvement in most of the wide range of cognitive functions typically affected in iNPH, with more severe functional deficits showing the greatest improvements, albeit without being completely restored to the levels recorded in healthy controls.

continued

Table III - (cont.)

AUTHORS	SAMPLE	METHODS	RESULTS
Saito et al., 2011	26 of 32 iNPH patients (mean age: 76.3 y)	Follow-up after one year. Neuropsychological evaluation: MMSE; memory (Digit Span, Spatial Span, Word recall and Word recognition subtest of ADAS); attention (TMT A); FAB; language (Object naming, Word fluency); visuospatial functions (Visual discrimination, Overlapping figures and Visual counting tasks).	Improvement in frontal functions (TMT and FAB)
Kazui et al., 2011	81 iNPH patients (mean age: 72.3 y)	Follow-up one year after shunt Caregiver burden scales	Decrease of caregiver burden
Koivisto et al., 2013	146 iNPH patients (mean age: 70.1 y)	Median follow-up 4.8 years Neuropsychological evaluation: MMSE; current intelligence (WAIS-R); memory (immediate and delayed wordlist, recognition of words, visual WMS-R); attention (TMT A/B, Stroop Test); psychomotor speed (tapping test)	117 patients (80%) had cognitive decline and 67 (46%) clinical dementia, mainly AD and vascular dementia.
Petersen et al., 2014	37 iNPH patients (mean age: 70 y)	Six months after shunt. Functional scales Scale for Quality of Life Caregiver burden scale	24 patients (65%) showed a clinical improvement, 31 (86%) showed improved quality of life which returned almost within normal range; caregiver burden was reduced only in caregivers to male patients.
Gözl et al., 2014	147 iNPH patients (mean age: 64 y)	Yearly follow-up examinations over six years Functional scales.	69 patients died during the follow-up; of 61 patients who reached the 6-year assessment, 59% had an excellent outcome, 15% satisfactory benefit and 26% unsatisfactory results.

Abbreviations: iNPH= idiopathic normal pressure hydrocephalus; AD=Alzheimer's disease; TMT A/B=Trail Making Test part A/B, MMSE=Mini-Mental State Examination; KOLT=Kendrick Object Learning Test; CANTAB=Cambridge Neuropsychological Test Automated Battery; FAB=Frontal Assessment Battery; ADAS=Alzheimer's Disease Assessment Scale; WMS-R=Wechsler Memory Scale-Revised; WAIS-R=Wechsler Adult Intelligence Scale-Revised; WMS=Wechsler Memory Scale; AVLT=Auditory Verbal Learning Test

Concluding remarks

The results of this literature review allow us to draw a series of observations. The cognitive impairment in iNPH has commonly been described as fronto-subcortical dementia, but the term is reductive as it does not fully describe the different clinical pictures observed. We still agree with the remarks of Iddon et al. (1999): "There may not be one single form of dementia syndrome in NPH but rather, there are varying degrees of cognitive change preshunt, according to the amount of permanent brain damage that has already taken place, compounded by comorbidity factors such as hypertensive cerebral small vessel disease". From this perspective it is also necessary to take into account the role of the "cognitive reserve" phenomenon (Stern, 2002), which may help to explain the great variability of cognitive impairment in iNPH. 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. As we underlined in the first main section of this article, the neuropsychological assessment has to include sensitive and exhaustive measures investigating the different cognitive domains. Moreover, a more detailed characterization of iNPH patients, particularly in terms of disease severity, is still lacking. We realize that it is not easy to establish with precision the different stages in the disease, nevertheless the studies reported in the literature have been conducted in patients with different disease durations and therefore with different degrees of disease severity, and obviously the results after shunt placement may well be negatively affected in patients with more severe or longer lasting disease. 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 iNPH remains a complex and underestimated disease. Clinical and neuroimaging

data are crucial for the diagnosis, but many other variables differently modulate and interfere with the disease expression. Undoubtedly, an overlap with other neurodegenerative diseases exists; this may be a complex and prognostic issue and could partly explain the progression of cognitive decline 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 have failed to obtain conclusive results. There is a need for further studies with longer follow-ups and also for closer interaction among the different professionals involved.

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