Spectrum of cognitive disorders in idiopathic normal pressure hydrocephalus

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Summary

Idiopathic normal pressure hydrocephalus (iNPH) is a complex syndrome first described by Adams et al. (1965) as ventricular dilation accompanied by a progressive triad of a gait disturbance, “dementia” and incontinence. Gait and balance disorders are the main clinical presentations, whereas cognitive decline appears 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 because of diagnostic challenges. Recent epidemiological studies report an increasing prevalence with increasing age, without difference between men and women, and confirm that this pathology is underdiagnosed (Jaraj et al., 2014; Martin-Láez et al., 2015). Guidelines and operating criteria for the diagnosis and management of iNPH have been proposed (Marmarou et al., 2005; Ishikawa et al., 2008; Mori et al., 2012, Williams and Relkin, 2013). The latter authors, in their detailed indications, stress the concept that the starting point should be a comprehensive history and neurological examination, review of neuroimaging, and evaluation of the differential diagnosis (Williams and Relkin, 2013).

The cognitive and behavioral disturbances accompanying iNPH have commonly been described as “frontosubcortical dysfunction” (Ogino et al., 2006; Tarnaris et al., 2011; Williams and Relkin, 2013). This clinical term is used to refer to a pattern of mental decline characterized by executive dysfunction, psychomotor slowing and mood symptoms, especially apathy. However, as reported in a recent review by Picascia et al. (2015), this definition is reductive, because it does not encompass the entire clinical spectrum. Patients with iNPH actually present impairment in broader cognitive domains: attention, working memory, episodic memory, visuoperceptual and visuospatial functions (Iddon et al., 1999; Walchenbach et al., 2002, Saito et al., 2011; Bugalho et al., 2014); some studies in particular have focused on posterior cortical functions, such as visuoperceptual and visuospatial functions.

The relationships between cognitive symptoms and other clinical variables in iNPH have not been completely defined; some authors found a positive correlation...
with motor disturbances (Golomb et al., 2000), while others failed to confirm this (Bugalho et al., 2014). In the present study we retrospectively evaluated cognitive profile, and its relationship with disease variables, in a group of subjects with iNPH.

Materials and methods

Materials

We retrospectively studied clinical charts collected from January 2010 to December 2014, at the Parkinson’s Disease and Movement Disorders Unit of the C. Mondino National Neurological Institute in Pavia, Italy. A case series of 64 subjects with a diagnosis of “probable” iNPH was collected. All the recruited patients had been referred to our unit with primary diagnoses of “parkinsonism”.

The diagnosis of iNPH was made on the basis of clinical, neuropsychological and neuroimaging features (Williams and Relkin, 2013). The main neuroimaging features were ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evans index > 0.3) and no macroscopic obstruction to CSF flow, and they 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 hippocampal atrophy; narrowing of the sulci and subarachnoid spaces over the high convexity-midline surface; a 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. All the patients had a positive spinal tap.

Evidence of a relevant antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus were excluded as were other neurological, psychiatric, or general medical conditions capable of explaining the symptoms.

Fifty-eight healthy elderly people, matched for age, sex and education, served as normal controls (NCs); these subjects were drawn from our historical archive of NCs recruited among hospitalized patients and/or patients’ relatives without neurological disorder or cognitive impairment.

All the patients and NCs were examined by a neurologist and tested by a neuropsychologist.

Methods

Evaluation of motor symptoms

Motor symptoms were evaluated using the Unified Parkinson’s Disease Rating Scale Part III (UPDRS III); this is a clinician-administered scale that is currently applied to measure the motor impairment due to parkinsonism (Goetz et al., 2008; Antonini et al., 2013).

Neuropsychological assessment

The following neuropsychological tests were administered to evaluate various cognitive domains:
- Mini-Mental State Examination – MMSE (Folstein et al., 1975): general index of cognitive functioning
- Digit Span forward, Word Span and Spatial Span – Corsi tests (Spinnler and Tognoni, 1987): working memory
- Rey’s 15-word test (Carlesimo et al., 1996), both immediate and delayed recall: long-term verbal memory
- Logical memory test (Spinnler and Tognoni, 1987): long-term verbal memory for structured material
- Raven’s Colored Matrices 47 (Carlesimo et al., 1996): visuospatial reasoning
- Weigl’s Sorting Test (Spinnler and Tognoni, 1987): categorical abstract thinking
- Frontal Assessment Battery – FAB (Apollonio et al., 2005): fronto-executive functioning
- Attentive matrices (Spinnler and Tognoni, 1987): selective attention
- Tests of phonological and semantic fluency (Carlesimo et al., 1996; Spinnler and Tognoni, 1987): lexical store
- Constructive Apraxia (Spinnler and Tognoni, 1987): copying and visuospatial abilities.

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

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, IL). Quantitative variables were described as means ± standard deviations (MsSD) and qualitative data as numbers and percentages. One-way analysis of variance (ANOVA) was used to detect significant differences between iNPH patients and HCs and between the different subgroups. Comparisons of percentages were performed using the chi-square test. For all analyses, the level of statistical significance was set at p<0.05.

Results

As reported in table I, in comparison with the NCs, the iNPH patients performed worse on almost all the neuropsychological tests, except for Rey’s 15-word test, immediate recall, and the Logical memory test, which were within the normal range.

Taking into account the different cognitive domains involved, and on the basis of equivalent scores, it emerged that the entire iNPH population could be subdivided into the following groups:
- group 1 (G1): 27 patients (42%) with global cognitive impairment, characterized by global deficit of cognitive
functions, or in any case by diffuse cognitive impairment;
- group 2 (G2): 15 patients (24%) with the more typical deficits in attention and executive abilities (frontosubcortical dysfunction);
- group 3 (G3): 11 patients (17%) with mild cognitive impairment, i.e. involving a single domain (isolated deficit of a single cognitive domain, e.g. memory, attention, visuospatial abilities);
- group 4 (G4): 11 patients (17%) with no cognitive impairment.

The clinical, demographic and motor characteristics of the different groups are reported in table II.

The G1 patients, compared with the other groups, were older, with a significantly longer disease duration and more severe motor impairment (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.

Discussion

The results of this study show that, in comparison with the controls, our entire iNPH population was impaired
in almost all neuropsychological measures; the extent of the statistical significance of the differences varied from test to test, being more pronounced in tests evaluating logical and executive functions. Only episodic memory was relatively preserved; these data seem to suggest that memory impairment in iNPH is generally milder compared with the impairment of other functions, executive ones in particular (Ogino et al., 2006). However, when we considered the different cognitive domains involved, we were able to identify subgroups of patients with different cognitive profiles: about half of the subjects (42%) presented a global-diffuse impairment which can be framed as dementia of mild to moderate degree. Among the patients classified as non-demented, only 24% presented frontosubcortical dysfunction; 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 literature data documenting a wide range of cognitive pictures in iNPH (Iddon et al., 1999; Walchenbach et al., 2002; Saito et al., 2011; Bugalho et al., 2014; Picascia et al., 2015); in particular, the definition “frontosubcortical dysfunction” is reductive as it does not encompass the entire spectrum of different cognitive profiles.

The second important finding of our study was the positive correlation detected between cognition and disease progression; in fact, although cognitive impairment may be absent in younger patients, it undoubtedly becomes more severe with older age, increasing disease duration and increasing severity of motor disturbances. This correlation points to the possible existence of a common pathophysiological mechanism. From this perspective, our data seem to suggest that early shunt surgery might be a way of limiting 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; this was indeed the reason they were referred to our unit. This aspect may represent a weakness of the study. On the other hand, it is well known that motor disorders are the main presentation of iNPH (Williams and Reilkin, 2013). In this study we administered an exhaustive neuropsychological test battery in order to investigate different cognitive domains; this is crucial for obtaining a detailed cognitive profile (Devito et al., 2005; Saito et al., 2011; Bugalho et al., 2014). In our opinion, accurate cognitive characterization of patients before shunt surgery is important from the perspective of outcome evaluation. Enrolling a homogenous population of iNPH patients may improve the prediction of response to shunt surgery. Furthermore, as previously underlined (Picascia et al., 2015), in this setting there is a need for further studies with longer follow-up periods and for closer interaction among the different professionals involved.

**References**


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