Chapter 14
Normal Pressure Hydrocephalus

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Abstract Although it has been nearly 50 years since its first description of clinical and radiological, there is considerable uncertainty about the diagnosis of normal pressure hydrocephalus because it shares the semiotics with the group of dementias. Hakim's triad (impaired gait, initially type clumsiness of the lower limbs followed over time by inability to ambulate or maintain an erect posture; cognitive impairment, initially limited to worsening deficits in memory fixation and execution of complex actions; the urinary disorder, initially type "urgent urination" and then complete urinary incontinence) characterizes the progressive course of the adult chronic hydrocephalus. The clinical onset is typically nonspecific, subtle, and most often monosymptomatic. The first diagnostic procedure is a head CT scan and/or brain MRI, which shows an abnormal dilatation of the lateral ventricles and the third ventricle, associated to variable brain atrophy. Not all subjects will develop a set of symptoms, since the altered cerebrospinal fluid dynamics can remain stable for many years or get progressively worse until the appearance of the clinical triad of normal pressure hydrocephalus. The test of intrathecal infusion (Katzman test) carried out at constant speed with the introduction of saline solution into the lumbar subarachnoid space and the concomitant detection of cerebrospinal fluid pressure establishes that patients with outflow resistance ranging from 12 to 19 mmHg/ml/min can improve clinically after surgery. This method requires extensive and prolonged experience of the center of application and the use of computer systems. The withdrawal of lumbar cerebrospinal fluid provides for the evacuation of 30–50 cc of

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cerebrospinal fluid by lumbar puncture under local anesthesia, preceded and followed by gait assessment and neuropsychological tests. It also uses the continuous withdrawal of CSF with an intrathecal catheter placed for 3 days, in order to drain approximately 135 ml/24 h and the aim of reducing false negatives. After surgery, the patient is usually able to regain a good quality of life, with independence in daily living activities. The duration of such postsurgical improvement is variable, but patients may improve again readjusting the opening pressure of the programmable valve, although a high comorbidity index is strictly related to a poor outcome.

Keywords Cerebrospinal fluid • Dementia • Gait abnormalities • Hydrocephalus • Idiopathic • Normal pressure • Programmable valve • Shunt • Urinary incontinence • Ventricle

Historical Remarks

In ancient times, hydrocephalus was associated to children with progressive enlargement of the head. Tapping the subcutaneous tissue of the frontal skin was the therapeutic procedure adopted for more than 2,000 years (Missori et al. 2010). Fabrizio d'Acquapendente was the first physician to perform a ventricular drainage in a child through insertion of a cannula in the frontal ventricle (Missori et al. 2011). The occurrence of hydrocephalus in adults, without increase of the head size, was a late clinical discovery. Pathological descriptions in the eighteenth and nineteenth centuries reported increase of "humor" in the ventricular system (Missori et al. 2010), but diagnosis in adults during life was impossible. The introduction of the withdrawal of cerebrospinal fluid (CSF) from the lumbar space in meningitic disease allowed the first therapeutic approach in adults affected by hydrocephalus (Wynter 1891). Hugo Wilhelm von Ziemssen considered the "spinal paracentesis" "an effective mean of reducing intracranial pressure in … hydrocephalus, … sometimes improvement in the subjective troubles and in the condition of the sensorium was striking and of long duration" (von Ziemssen 1893). Since then, withdrawal of CSF in patients with chronic hydrocephalus or increased intracranial pressure was extensively performed (Albert 1918; Browning 1897; Greenfield 1935; MacCordick 1922; Rhodes 1903). The introduction of the ventriculography by Dandy (Dandy 1918) allowed the radiological diagnosis of pediatric hydrocephalus (Dandy 1918), and later Evans introduced a ratio to differentiate normal from hydrocephalic children (Evans 1942). In 1949, the first cerebrospinal pediatric shunt was applied by Matson, Nulsen, and Spitz (Matson 1949; Nulsen and Spitz 1951). In that time, the diagnosis of secondary hydrocephalus in adults was limited to patients with brain tumors and post-traumatic or post-meningitic hydrocephalus. In the mid-1960s, Adams and Hakim demonstrated in three adults with hydrocephalus (primary in one and post-traumatic in two) associated to typical neurological features that withdrawal of 15–20 ml of CSF determined a marked clinical improvement (Adams et al. 1965). The subsequent surgical ventriculoatrial shunt allowed a definite clinical improvement. Since then

the pressure of the CSF was in the normal range, the disease was named "normal pressure" hydrocephalus (NPH). For some years, the term was unchanged, but due to the unknown origin of the disease, the term "idiopathic" NPH was added (Black 1980; Greenberg et al. 1977; Shenkin et al. 1975). During the second half of the twentieth century, the diagnostic and therapeutic procedures of withdrawal of CSF became more common after the introduction of spinal catheters and continuous CSF drainage (Aitken and Drake 1964; Matera and Althabe 1962; Vourc'h 1963; Vourc'h and Rougerie 1960). The advent of computed tomography represented a milestone of the radiological diagnosis (Gunasekera and Richardson 1977; Jacobs and Kinkel 1976), with a transposition of the Evans' index values for hydrocephalus' diagnosis from the pneumoencephalography (Gawler et al. 1976; Synek et al. 1976). A further progress came with the "Charles Miller Fisher test," in which clinical improvement persisted many months after a single 20–30 ml CSF tap in patients with NPH (Fisher 1978). This procedure was considered more effective if extended to more days (Di Lauro et al. 1986). Katzman was the first to suggest an infusion of physiologic solution into the lumbar subarachnoid space, with monitoring of CSF pressure (Katzman and Hussey 1970). After infusion of physiologic solution into the lumbar subarachnoid space and monitoring CSF pressure, the capacity to absorb additional physiologic solution was reduced in patients with NPH and the CSF pressure quickly increased. The last remark in this history is the guidelines for the diagnosis and management of idiopathic normal pressure hydrocephalus which came to light from an international group of researchers in 2005 (Marmarou et al. 2005b). In a five-step document, all the solved and unsolved questions were addressed, to offer an essential reference from which prospective randomized studies could originate.

Introduction

The CSF is produced by the choroid plexuses of the lateral and fourth ventricles and from the capillary ultrafiltrate of the Virchow-Robin spaces, at a rate varying between 0.2 and 0.6 ml per minute or 600 and 700 ml per day (Wright 1978). This amount of fluid is reabsorbed through three main systems: the arachnoid villi into the cerebral venous sinuses, the subarachnoid space along thoracic and lumbosacral spinal rootlets, and the olfactory pathway (Edsbagge et al. 2004; Johnston 2003; Luedemann et al. 2002; Mollanji et al. 2002). The equilibrium between production and reabsorption allows normal ventricle size during life, and every pathological condition which alters this CSF balance can produce progressive ventricular enlargement, up to hydrocephalus. This simple concept is challenged by some brain degenerative disorders (i.e., Alzheimer's disease, progressive supranuclear palsy, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, Parkinson's disease), in which a progressive tissue loss is replaced by CSF. In these patients, the atrophy of the brain is the primary event and the increase of the amount of CSF results from neuronal loss. The characteristic secondary ventricular enlargement resembles moderate hydrocephalus, but the clinical picture must be carefully

Table 14.1a Prevalence of adult chronic idiopathic hydrocephalus in the literature

	Prevalence (%)	Sample	Criteria for the diagnosis of NPH
Fisher (1982)	4	Dementia	Clinical
Casmiro et al. (1989)	0.5	2 out of 396 subjects over 65 years	Clinical
Trenkwalder et al. (1995)	0.5	4 out of 982 patients with Parkinson's disease	Clinical
Bech-Azeddine et al. (2001)	3.5	14 out of 400 patients of a memory clinic	Clinical
Clarfield (2003)	1	50 out of 5,000 patients with dementia	Clinical
Marmarou et al. (2007)	11.56	17 out of 147 dementia	Clinical-radiological
Brean and Eide (2008)	0.022	21.9 per 100,000 adults	Clinical-radiological
Hiraoka et al. (2008)	7.6	13 out of 170 adults over 65 years	Radiological
Tanaka et al. (2009)	1.4	7 out of 7,497 adults over 65 years	Clinical-radiological

evaluated together with neurological examination and brain imaging, since the correct diagnosis of NPH is promoted by additional tests. Other conditions which may resemble the clinical picture of NPH (either in early stages or later in the course of the primary disease) include secondary post-traumatic or posthemorragic hydrocephalus, systemic lupus erythematosus, and rarely neurosarcoidosis (Honda et al. 2004; Westhout and Linskey 2008; Wikkelsø et al. 1982). In these conditions, the clinical course is characterized by faster progression, unlike in NPH patients. Other rare conditions in which an NPH can occur are myotonic dystrophy and Paget's disease (Christensen 1988; Delavallée and Raftopoulos 2006; Martin et al. 1985; Moiyadi et al. 2006; Riggs et al. 1985; Roohi et al. 2005).

Epidemiology

Currently, the prevalence and incidence of NPH cannot be determined precisely, although probably it is a common disease and its prevalence increases with age (Conn 2011; Marmarou et al. 2005b). It is assumed that NPH roams to about 4 % of all dementias (Fisher 1982). The results of various studies providing data about prevalence and incidence of NPH are reported in Tables 14.1a and 14.1b. The diagnosis is also strongly influenced by the criteria used to establish the diagnosis of NPH.

A study carried out in San Marino in a population of 396 people over 65 identified two patients with NPH, with a prevalence of 0.5 % (Casmiro et al. 1989). Similarly, a German door-to-door investigation on motor disorders in parkinsonism detected four patients with NPH out of 982 subjects (Trenkwalder et al. 1995). According to a census of 2000 in the USA reporting about 35 million people over 65, a 0.5 %

Table 14.1b Incidence of adult chronic idiopathic hydrocephalus in the literature

	Incidence		Criteria for the diagnosis of NPH
Vanneste et al. (1993)	0.13–0.22	100,000/year	Clinical
Krauss and Halve (2004)	1.8	100,000/year	Clinical-radiological
Tisell et al. (2005)	1–3	100,000/year	Clinical-radiological
Brean and Eide (2008)	5.5	100,000/year	Clinical-radiological

prevalence of NPH would result in a number of approximately 175,000 patients affected by NPH (Suzuchi et al. 2000), while a 12 % prevalence of Alzheimer's disease would result in 4.5 million of patients. A study conducted in a sample of 400 patients of a memory clinic (Gunasekera and Richardson 1977) detected 14 patients (3.5 %) suffering from IICA (Bech-Azeddine et al. 2001). In a meta-analysis of 37 studies on dementia, the prevalence of adult chronic idiopathic NPH in 5,000 patients is about 1 % (Clarfield 2003). Accordingly, among patients with dementia in the USA (between four and six million), the number of patients with NPH may range between 40,000 and 60,000 (Hebert et al. 2003). These estimates may increase by four times (160,000–240,000 patients) if we refer to a prevalence of 4 % of NPH reported by other studies (Relkin et al. 2005). A recent investigation, performed in the USA on a population of 147 patients, reported a prevalence of 11.56 % of patients suffering from NPH (Marmarou et al. 2007). Recent studies performed on healthy population showed a sharp increase in the prevalence of the NPH. In Norway, a study of 100,000 people identified 21.9 cases (Brean and Eide 2008), while a Japanese work detected an incidence ranging from 2.9 (clinical and radiological diagnosis) to 7.6 % (radiological diagnosis only) in the healthy population of over 65 years (Hiraoka et al. 2008). In Italy, according to a survey carried out in November 2006, people over 65 years accounts for about 20 % of the population (about 11 million out of a total of 56 million) (Colitti et al. 2006). Accordingly, the estimated number of NPH patients may be about 55,000. A retrospective study performed in the USA showed that in 2000 the number of NPH patients treated by drainage was only 5,547 per year, suggesting that a limited number of patients are diagnosed and then treated, as compared to the potential number of subjects to be treated (Patwardhan and Nanda 2005). Vanneste has estimated that the incidence of patients with NPH in the Netherlands might be between 1.3 and 2.2 per million per year (Vanneste et al. 1993). Krauss in Germany calculated an incidence of 1.8 per 100,000 per year (Krauss and Halve 2004). Finally, a Swedish study reported that the use of derivative systems for patients with NPH is around 30 % of all shunt surgery, which is between only 3 and 6 per 100,000 people (Tisell et al. 2005). In Norway, however, a recent study in 2008 reported an incidence of 5.5 patients with NPH per 100,000 per year (Brean and Eide 2008). Since histological studies show lesions consistent with Alzheimer's disease in brain biopsies of patients with NPH, the coexistence of two diseases leads to underestimate the right number of patients with NPH (Chakravarty 2004; Silverberg et al. 2003). Thus, it might be speculated that NPH may occur in 15–20 % of demented patients (Relkin et al. 2005). In Italy, the prevalence of patients with NPH might be around 836,000 (7 % of the Italian

population over 65 years). As in the next decades an overall aging of population is expected (in 2050, 33 % of the Italian population will be over 65 years), this will result in a progressive increase in the number of patients with NPH.

Familial Normal Pressure Hydrocephalus

Few studies reported a possible familial association in NPH (Portenoy et al. 1984). The description of a large family with four members showing a late-onset primary NPH across three generations suggests the opportunity to search for underdiagnosed and asymptomatic NPH in adult family members of patients with NPH (Takahashi et al. 2011). An autosomal dominant transmission has been hypothesized. Another study reported two sisters with clinical and radiological features of NPH, who underwent shunt placement with clinical improvement (Cusimano et al. 2011). In both sisters, an epsilon3-epsilon3 genotype of the apolipoprotein E (ApoE) on chromosome 19 was detected. Familial aggregation of NPH among first-degree relatives is suggested by an incidence of 7.1 and 0.7 % among control relatives (McGirr and Cusimano 2012).

Clinical Picture

The most characteristic picture in patients with NPH is the Hakim's triad: gait disturbance, urinary incontinence, and cognitive decline (Adams et al. 1965). Gait disturbances may occur as the first symptom and vary in the course. In early phases, the patient may complain of a slow, wide-based walking with small steps and sudden drops, charged to the shoes or uneven floor (McHugh 1964; Missori et al. 2010; Roger et al. 1950). In later stages, a cane or wheeled walker may be needed. In late stages, due to tendency to fall, the patient is completely unable to walk. Differentiating between Parkinson's disease and NPH can be challenging for the practicing clinician; in NPH usually the motor impairment is mainly confined in the lower limbs (*lower-body parkinsonism*) and the response to levodopa is poor or absent, but in some cases, the differential diagnosis may not be so straightforward (Table 14.2). Dopamine transporter brain imaging (*DaTSCAN*) using single-photon emission tomography (SPECT) may be useful, since it shows an abnormal picture in all cases of PD, while the uptake is usually normal in NPH. Disturbances of micturition usually appear in association with other symptoms of NPH. In early stages NPH patients often complain daily need to urinate more often than usual, sometimes with urgency. When the disease worsens, occasional incontinence happens. This symptom is very harmful to patients and relatives, and in males the attention is often focused on prostatic function and sometimes surgery is even carried out to treat urinary symptoms. In patients with NPH SPECT, studies showed that urinary dysfunction may be closely related with right frontal cerebral hypoperfusion, the most common urodynamic abnormality being detrusor overactivity (Sakakibara et al. 2008, 2012).

Table 14.2 Differences between normal pressure hydrocephalus and Parkinson's disease gait

Features	Normal pressure hydrocephalus	Parkinson's disease
Early stages	May occur as the first symptom Clumsiness of the lower limbs	Usually not the first symptom Subtle, if present Loss of unilateral arm swing
Middle stages	Wide-based walking	Normal or narrow-based walking
	Small steps	Small steps
	Stooped stance	Stooped stance
	Sudden drops	Sometimes, festination and freezing
	Charged to the shoes or uneven floor	
	Outward rotated feet and a diminished height of the steps	
	Frequent freezing	
Late stages	Tendency to fall	Tendency to fall
	Inability to ambulate or maintain an erect posture	Inability to ambulate or maintain an erect posture
	Frequent freezing	Frequent festination and freezing
Speed	Slow	Slow
Stride length	Reduced	Reduced
Rhythmicity	Reduced	Reduced
Symmetry	Reduced	Reduced
Improvement with external clues	Mild	Moderate
Response to levodopa	None or mild	Moderate

Cognitive and behavioral symptoms are key clinical features of NPH and may appear in early disease stages (Hashimoto et al. 2010). In individual patients with NPH, however, the cognitive impairment may vary largely, ranging from a mild cognitive decline to a moderate or severe dementia in other patients.

Various neuropsychological studies have supported the view suggesting that patients with NPH may frequently show a "subcortical" pattern of cognitive impairment (Cummings and Benson 1984; Devito et al. 2005), which is often seen in pathologies affecting various subcortical structures and is mainly characterized by the occurrence of mental slowness, deficits of attention and frontal executive functions (planning, problem-solving, set-shifting), relatively mild deficits of long-term memory, and behavioral changes (apathy most frequently, depressive symptoms in some patients). Since deficits of executive functions frequently arise from a dysfunction of the frontal lobes, which are abundantly connected to various subcortical structures (Alexander et al. 1986), the term "frontal-subcortical" cognitive impairment/dementia has also been proposed. Such most frequently reported "frontal-subcortical" pattern of cognitive impairment observed in patients with NPH does usually not include aphasic, apraxic, or agnostic deficits, which are by contrast common in patients with "cortical" dementias (*in primis*, Alzheimer's disease). As to long-term memory deficits, it has been shown that patients with NPH

in early disease stages have usually a relatively preserved ability to store information in long-term memory systems (at variance with patients with Alzheimer's disease since early disease stages), but are usually impaired mostly in the retrieval of stored information from long-term memory systems and therefore may benefit from external cues aimed at facilitating such retrieval (Iddon et al. 1999). This pattern of memory impairment of NPH patients may be shared by other conditions with a "frontal-subcortical" pattern of cognitive impairment, such as Parkinson's disease (Taylor et al. 1986). In addition, deficits of spatial long-term memory (Iddon et al. 1999), constructional praxic abilities (Goodman and Meyer 2001), and psychomotor speed (Kaye et al. 1990) have been detected in patients affected by NPH.

In a recent study (Saito et al. 2011) aimed at further investigating cognitive functioning in patients affected by idiopathic NPH, 32 patients with NPH who significantly improved after surgery were recruited and underwent a quite extensive neuropsychological assessment before ($n=32$) and 1 year ($n=26$) after CSF shunt surgery. Moreover, a group of patients with Alzheimer's disease ($n=32$) matched to the NPH group as for several clinical and demographic variables (including overall cognitive functioning as measured by performance on the mini-mental state examination, MMSE) and a group of healthy controls (HCs) ($n=30$) were recruited. The results of such study show that patients with NPH showed a significantly worse performance as compared to healthy controls on most cognitive tasks (MMSE, tasks of verbal and spatial short-term memory, phonological and semantic verbal fluency, episodic verbal memory, several tasks assessing visual discrimination, and the Frontal Assessment Battery (FAB) assessing executive functions), while no significant difference was found between the NPH and HCs on a task of object naming. Moreover, the NPH group performed significantly worse than the AD group on some cognitive tasks (spatial short-term memory, phonological verbal fluency, FAB, some tasks assessing visual discrimination), while the AD group was more impaired than the NPH group on specific cognitive variables assessing episodic verbal memory. Although deficits of frontal cognitive functions (including executive functions) were the most prominent in the NPH group, this study pointed out that memory deficits and visuoperceptual and visuospatial deficits may also occur in patients with NPH. This recent study (Saito et al. 2011) suggests that, although deficits of frontal cognitive functions (including executive functions) due to a disruption of frontal-subcortical circuits are the most prominent in patients with NPH, memory deficits and visuoperceptual and visuospatial deficits (due to a disruption of neural circuits involving more "posterior" cortical and subcortical structures) may also occur in patients with NPH.

As to other behavioral symptoms (Bloom and Kraft 1998; Kito et al. 2009; Koch et al. 2009), besides apathy and depression, it has been less commonly reported that patients with NPH may show manic and psychotic symptoms (Kwentus and Hart 1987; Rice and Gendelman 1973), including aggressivity, hypersexuality, and delusional jealousy (Yusim et al. 2008).

A distinguishing feature of NPH is the relatively slow but progressive clinical evolution (12–24 months), as the patient becomes unable to carry out everyday activities and to look after himself. However, some patients may show a slower

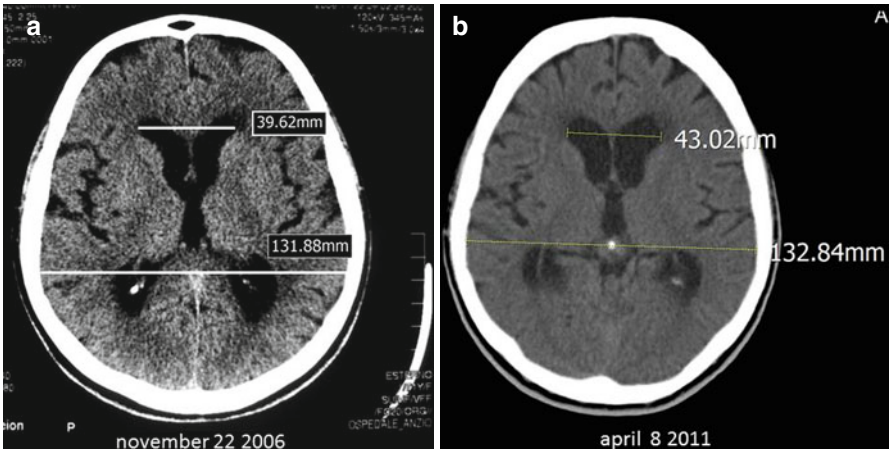

Fig. 14.1 (**a**) A 72-year-old female with gait instability. CT scan shows Evans' index of 39.62 mm/131.88 mm = 0.30. (**b**) The same patient after 55 months complaining short memory impairment, recurrent falls, and urgent urination. On control CT scan the frontal horns appear more enlarged with Evans' index increase: 43.02 mm/132.84 mm = 0.32

clinical progression both for very mild symptoms and for misdiagnosis. In these patients, neuroimaging commonly shows a ventriculomegaly. When acute or subacute symptoms of intracranial pressure (headache, alteration of consciousness, cranial nerve deficits, vomiting, dizziness) occur in a short period of time (1–2 weeks) associated to brain scan of ventricular enlargement, a secondary hydrocephalus other than NPH or a cerebrovascular disease should be considered as the causative condition. In the cases in which a previous neuroradiological imaging is available, a comparison of the Evans' index between the old and new examination allows a more secure and reliable assessment of the ventricular progression and of clinical diagnosis (Figs. 14.1 and 14.2).

Scales for Grading of Severity

Various grading scales have been reported for assessment of patients with NPH. The use of functional scales based on the degree of disability or stroke rehabilitation scales have been proposed, but these scales were not devised to assess changes in the severity of main symptoms of NPH (Klinge et al. 2005). The need to develop assessment scales to be largely shared in the clinical evaluation of patients with NPH prompted the proposal of two new grading scales (Hellström et al. 2012; Kubo et al. 2008). A major advantage of both scales is the possibility to compare the neurological conditions before and after each diagnostic or therapeutic procedure. Cognitive, gait, and urinary symptoms are assessed in both scales (Hellström et al. 2012; Kubo et al. 2008), while the examination of balance only in one (Hellström et al. 2012). In the Swedish scale (Hellström et al. 2012), three different professionals evaluate

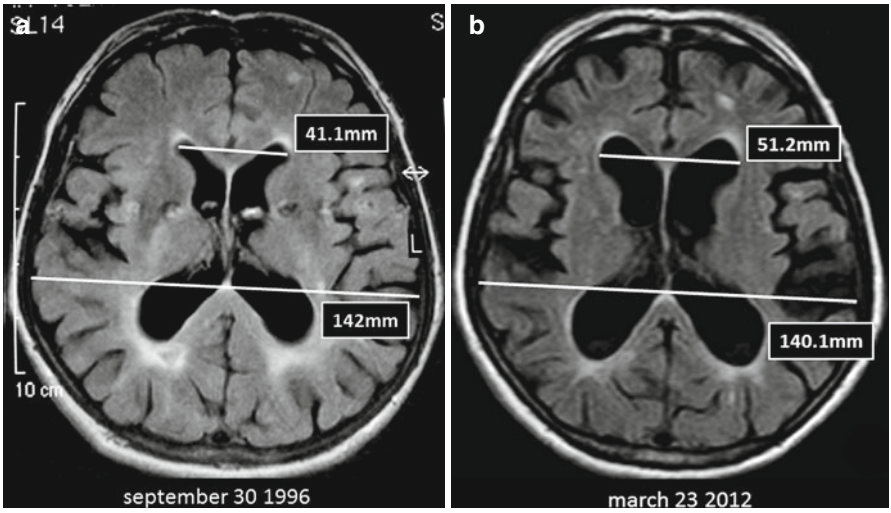

Fig. 14.2 (**a**) A 61-year-old female with short-term memory deficit. MRI shows Evans' index of 41.1 mm/142 mm = 0.28. (**b**) The same patient after 16 years with mild cognitive impairment, progressive gait disturbance, and occasional urinary incontinence: Evans' index of 51.2 mm/140.1 mm = 0.36. Note the secondary brain atrophy with widening of the Sylvian cisterns

separately the three main groups (cognitive, gait, urinary) of symptoms, and scores may range from 0 to 100, where 100 is the performance of an age-matched healthy population. Such scale discriminates well between levels of severity. Following surgery, a patient is considered improved if a >5-point increment can be detected on the scale. In the Japanese scale (Kubo et al. 2008), the clinical assessment is performed by two independent physicians. Patients with NPH were assessed with this scale after a CSF tap test and after shunt surgery. For the triad of symptoms, scores may range from 0 to 4, with higher scores indicating more severe symptoms. Patients who obtain an improvement in at least 1 of the 3 domains are judged to have a clinically significant improvement. Reliability and validity in predicting shunt responsiveness were assessed for this scale.

Neuroradiological Evaluation

On computed tomography (CT) or magnetic resonance imaging (MRI), the radiological finding of ventricular enlargement is a necessary landmark of NPH, but it is not sufficient to determine if patients are suffering from NPH. In neurodegenerative diseases, cerebral atrophy causes secondary ventricular enlargement and a radiological differential diagnosis with NPH can be problematic. The first step in the evaluation of an image must be the computation of the Evans' index, by dividing the maximum width of the frontal horns by the maximum width of the inner table of

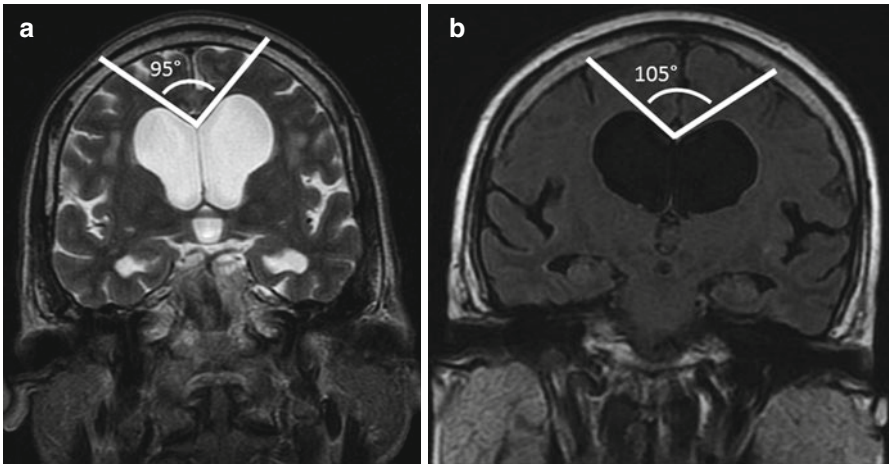

Fig. 14.3 (**a**) A 67-year-old male with slight cognitive impairment, progressive gait disturbance, and occasional urinary incontinence. Neuroradiological examinations from July 1993 show progressive ventricular enlargement. In the last MRI (June 2012), the Evans' index is 59.4 mm/137.60 mm = 0.43, and on T2 coronal image at the level of the posterior commissure, the callosal angle is more than 90°. After a positive tap test, a programmable shunt was inserted. Ten months after surgery the patient has a lasting clinical benefit on gait disturbance and urinary incontinence. (**b**) A 64-year-old female with gait instability and urinary incontinence. On MRI the Evans' index shows 47.4 mm/127.1 mm = 0.37. On coronal T1 image at the level of the posterior commissure, the callosal angle is more than 90°. Two years after surgery the patient is asymptomatic. The callosal angle must be interpreted in association to the clinical symptoms and all the neuroradiological findings

the cranium at the level of the Monro's foramens in the frontal horns (Evans 1942). A value equal or more than 0.3 support the diagnosis of probable NPH (Ishikawa et al. 2008; Marmarou et al. 2005b), but a lower value cannot exclude this diagnosis (Naruse and Matsuoka 2013). After shunt for NPH, the majority of the patients assessed by the Evans' index showed no ventricular changes, despite a satisfactory clinical improvement (Meier et al. 2003). Since remarkable differences were found in the Evans' index calculated at different planes on CT scans, its value has been questioned and not considered an ideal tool for diagnosis of NPH (Ambarki et al. 2010; Toma et al. 2011a). Other simple criteria which support a radiological diagnosis of NPH include a tight high-convexity and medial subarachnoid spaces, enlarged Sylvian fissures, a small callosal angle (under 90°) on the coronal section of MRI, and periventricular signal changes (Fig. 14.3) (Hashimoto et al. 2010; Ishii et al. 2008; Kitagaki et al. 1998; Sasaki et al. 2008). The aqueductal CSF stroke volume, which is the mean volume of CSF passing through the Sylvian aqueduct during cardiac systole and diastole, is a valuable tool in the preoperative evaluation of NPH patients. Higher aqueductal stroke volume in patients with short clinical history may be associated to a post-shunt improvement of clinical symptoms (Bradley et al. 1996; El Sankari et al. 2012; Scollato et al. 2009). The assessment of the ventricular size and volume may show very variable changes and may not easily correlate with

clinical improvement after CSF withdrawal (Anderson et al. 2002; Lenfeldt et al. 2012; McConnell et al. 2004; Palm et al. 2006). However, if the ventricular and brain volumes are assessed with a specific software, after prolonged external lumbar drainage, the brain volume may increase and the ventricular volume may decrease, more markedly than after a single tap withdrawal (Singer et al. 2012). A study with functional MRI in NPH patients showed a bilateral increased activation in the supplementary motor area after CSF removal (Lenfeldt et al. 2008b). Moreover, proton magnetic resonance spectroscopy revealed normalization of N-acetyl-aspartate in the frontal white matter after a 3-day lumbar drainage (Lenfeldt et al. 2008a).

The Supplemental Tests

The lack of a confident radiological diagnosis of NPH prompted the investigation of other diagnostic tools. Three diagnostic procedures are widely carried out: the withdrawal of lumbar CSF (30–50 ml), the external lumbar drainage (a 3-day drainage of approximately 135 ml/24 h), and the infusion test (lumbar infusion bolus technique: 4 ml, 1 ml/s). The choice among such options seems to be fundamentally related to the experience of each single center or clinician, more than to evidence-based studies, since these tools can be used for selecting patients for shunt surgery, but not for excluding patients from treatment (Wikkelsø et al. 2013). Comparisons among these procedures have been carefully investigated in various studies, highlighting advantages and disadvantages (Marmarou et al. 2005a). It should be pointed out that when the clinical and radiological diagnosis of NPH is highly probable, shunt surgery may be recommended also in the absence of supplemental tests, with a degree of certainty ranging from 50 to 61 % (Klinge et al. 2012; Marmarou et al. 2005a). However, it is recommended that all patients with probable or possible NPH should perform one of these tests, in order to obtain a probability measure of a successful response to shunt surgery, beyond such 50–61 % degree of certainty. The tap test has a higher positive predictive value (100 %) for a good response to surgical shunt, but a low sensitivity (from 21 to 61 %). A negative tap test cannot exclude patients from surgical treatment. The removal of CSF may improve gait or cognitive performance neuropsychological tests. The external lumbar drainage shows high sensitivity (50–100 %) and high positive predictive value (80–100 %). This procedure requires a hospitalization for some days, but in some patients may be complicated by replacement of escaped lumbar drain and, rarely, by secondary meningitis. Changes in walking pattern or neuropsychological tests are important variables to be assessed before and after CSF removal. In particular, an improvement of gait (speed, number of steps, stride length) is considered that may predict a good postsurgical outcome, suggesting the opportunity of a surgical treatment (Matousek et al. 1995; Damasceno et al. 1997; Stolze et al. 2000; Virhammar et al. 2012; Wikkelsø et al. 1982). As compared with the tap test, the CSF resistance outflow test has a similar positive predictive value (75–92 %), but a higher sensitivity (57–100 %). To perform this test, the baseline cerebrospinal pressure must be recorded before and immediately after injection. Patients with a threshold of CSF

outflow resistance ranging from 12 to 19 mmHg/ml/min seem to improve clinically after surgery, but there is still disagreement about the exact value to be considered pathological (Czosnyka et al. 2003). This procedure can be performed to assess the failure of a third ventriculostomy or of a surgical shunt (Aquilina et al. 2012; Malm et al. 2004).

The Surgical Treatment

Clinical evidence supports the value of surgery in NPH patients, despite the lack of randomized controlled trials comprising surgical treatment versus no surgery (Esmonde and Cooke 2002; Toma et al. 2011b, 2012). The best surgical technique to treat NPH should be aimed at obtaining a diversion of flow of CSF and at favoring the impaired processes involved in CSF reabsorption. There are two surgical options to enable such events: the endoscopic third ventriculostomy and the placement of a CSF shunt from a cerebral ventricle into an absorbing cavity or the vascular system. The endoscopic third ventriculostomy is performed through a frontal burr hole. The endoscope is inserted in the brain to gain the Monro's foramen and the floor of the third ventricle. After the identification of landmarks (the mammillary bodies and tuber cinereum), a catheter pierces a chosen place to put CSF flow between the interpeduncular cistern and the third ventricle. A low complication rate, a low mortality rate, and good neurological improvement are reported (Bouras and Sgouros 2012; Fountas et al. 2012; Gangemi et al. 2004, 2008). Since in the long-term follow-up closure of the fenestration and recurrent symptoms after initial successful treatment occur, these patients should be monitored for some years (Amini and Schmidt 2005; Cage et al. 2011; Fabiano et al. 2010; Longatti et al. 2004). A randomized clinical trial comparing the endoscopic third ventriculostomy with the ventriculoperitoneal shunt (shunt into the abdominal cavity) shows that the shunt has a better neurological outcome 12 months after surgery (Pinto et al. 2013). Indeed the surgical shunt is the most widely performed procedure to treat the NPH. Over the past few decades, the rate of complications after surgical treatment has decreased considerably, due to the improvement of the techniques and valve systems (Black 1980; Farahmand et al. 2009; Greenberg et al. 1977; Larsson et al. 1991; Poca et al. 2004; Savitz and Bobroff 1999; Zemack and Romner 2008). The ventriculoperitoneal shunt is more widely performed as compared with the ventriculoatrial shunt, probably due to early reports indicating a less risk of serious complications and neurosurgeon's confidence for the abdominal insertion in pediatric patients (Keucher and Mealey 1979; Mazza et al. 1980; Olsen and Frykberg 1983; Vernet et al. 1993). This conclusion has been initially transferred to adult patients (Lam and Villemure 1997). More recent surgical series show no difference between ventriculoperitoneal and ventriculoatrial shunt in adult hydrocephalus, and in some cases ventriculoatrial shunt is carried out after a failure of the ventriculoperitoneal shunt (Farahmand et al. 2009; Murakami et al. 2010; Stranjalis et al. 2012; Zhang et al. 2009). An alternative surgical option in patients with NPH is the lumboperitoneal shunt (Bloch and McDermott 2012; Chang et al. 1999; Yadav et al. 2010). Since NPH is a communicating hydrocephalus, it is

possible to drain the lumbar CSF into the abdominal cavity, through an intrathecal spinal catheter, with a programmable valve. The technique is apparently simple, but the rate of complication is not low (Karabatsou et al. 2004; Wang et al. 2007). The ventriculopleural shunt (into the space between the visceral and parietal pleura of the lungs) is very rarely performed in patients with NPH and is indicated when other routes are not available (Megison and Benzel 1988). The introduction of programmable (flow-regulated) versus nonadjustable (differential-pressure) valves has changed the surgical view: the amount of CSF withdrawal can be varied according to the clinical changes which can occur in the early or late postoperative follow-up (Zemack and Romner 2000). Readjusting the opening pressure may decrease the incidence of clinical complications of underdrainage or overdrainage (Freimann and Sprung 2012). A low CSF pressure has been proven to have a better outcome, but it is plagued by overdrainage complications (Boon et al. 1998). Accordingly, the combination of programmable valve with a gravitational valve (which eliminates overdrainage by increasing resistance as patient moves upright) may improve the outcome (Lemcke and Meier 2010; Meier and Lemcke 2006). A recent trial showed that a gravitational valve (which switches between a low pressure mode in the supine position and a high pressure mode in the upright position) reduces the risk of overdrainage complications, as compared with a standard programmable valve (Lemcke et al. 2013).

Outcome

The most relevant feature of patients who undergo surgical treatment for NPH is the rapid neurological improvement in the early postoperative period. In the majority of cases, patients regain the ability to walk and control micturition but also, albeit less frequently, of cognitive and behavioral symptoms. Accordingly, NPH is included among the infrequent conditions of reversible dementia. In particular, it has been observed that deficits of episodic verbal memory (Gallassi et al. 1991), constructional praxic abilities (Goodman and Meyer 2001), and psychomotor speed (Kaye et al. 1990) may improve after shunt surgery, at least in subgroups of NPH patients. On the other hand, it has been reported that deficits of executive functions may not improve after surgery (Iddon et al. 1999). By contrast, in a more recent study (Saito et al. 2011), 1 year after CSF surgery, the NPH group showed a significant improvement on tasks assessing frontal functions (FAB), including executive functions.

In a recent neuropathological study (Cabral et al. 2011), a group of nine patients with a clinical diagnosis of NPH was examined, and it was observed that in eight out of such nine patients, there were neuropathological changes consistent with AD. This study on a small sample of patients with a clinical diagnosis of NPH suggests that AD may be a frequent pathological comorbidity in patients with NPH and such comorbidity may at least partially preclude cognitive improvement after surgery.

A study carried out in 36 patients with NPH (Chang et al. 2006) who underwent neuropsychological testing before and after ventriculoperitoneal shunt insertion reported that one third of patients showed good cognitive improvement (defined as improvement by at least 25 % on at least half of the cognitive tests administered).

The degree of cognitive improvement was found to be greater in women than in men, and there was a significant negative linear relationship between age and probability of good cognitive improvement. Younger age was found to be a better predictor of improvement on memory tests, while female sex was a better predictor of improvement on non-memory tests after shunt insertion (Chang et al. 2006).

In conclusion, an extensive neuropsychological assessment in patients with suspected NPH may show the pattern of cognitive impairment in each individual patient and could be a helpful tool in the differential diagnosis of NPH, in monitoring disease progression, and in assessing clinical response to surgery (Devito et al. 2005).

After surgery, the patient is usually able to regain a good quality of life, with independence in daily living activities. The duration of such postsurgical improvement is still difficult to be predicted. At least a 1-year post-shunt monitoring period may be necessary to evaluate the clinical effects of the surgical procedure (Klinge et al. 2005, 2012). However, some shunted NPH patients experience years after surgery a variable decline and recurrence of symptoms, but after readjusting the opening pressure of the programmable valve (increasing the outflow of CSF), patients may improve again (Aygok et al. 2005; Koivisto et al. 2013). Accordingly, a periodic clinical follow-up is mandatory to avoid delays in the valve adjustment. Several studies showed that comorbidities (mainly cardiovascular and cerebrovascular disorders) may affect significantly long-term outcome in shunted patients with NPH (Kiefer et al. 2006; Lemcke and Meier 2012; Malm et al. 2013; Meier and Lemcke 2008, 2010; Mirzayan et al. 2010), suggesting that a high comorbidity index is strictly related to a poor outcome (Lemcke and Meier 2012; Mirzayan et al. 2010).

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