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Clinical Diagnosis and Treatment Management of Normal Pressure Hydrocephalus

Hüseyin Yakar

Abstract

Inadequate absorption of cerebrospinal fluid (CSF) at the arachnoid granulation level during circulation results in an increase in CSF in the ventricle and certain neuropsychiatric clinical findings. This syndrome, which often presents with ventricular dilatation, progressive cognitive decline, walking difficulties, and urinary incontinence symptoms in elderly individuals, is called Normal Pressure Hydrocephalus (NPH). It is projected that as people's quality of life improves and their life expectancy rises, more old people would develop this condition. Although a clear clinical triad has been defined, the identification of patients with NPH and the application of effective treatment modalities still pose a number of challenges for neurosurgeons today. However, despite all these difficulties, if diagnosed and treated early, the unusual appearance of these symptoms affecting elderly individuals can be prevented and significant improvements in quality of life can be achieved.

Keywords: normal pressure hydrocephalus, elderly individuals, neurodegenerative diseases, cognitive deficits, early surgical treatment

1. Introduction

The brain and spinal cord are soft and vulnerable structures by their very nature. Cerebrospinal fluid (CSF) is the air cushion of the central nervous system (CNS), which protects the nerve tissue by reducing the speed of the blows to the CNS. 90% of this fluid is produced continuously by specialized cells called choroid plexus in the ventricle and 10% by ependymal cells lining the ventricle surface. CSF, which flows through F. Luschka and F. Magendie into the subarachnoid space to surround the brain and spinal cord, drains into the venous system via arachnoid granulation. Colombian neurosurgeon Hakim et al. [1–3] described a clinic in 1964 characterized by progressive cognitive decline with ventricular dilatation (normal CSF pressure during lumbar puncture), difficulty walking, and urinary incontinence syndrome. Hakim named this syndrome Normal Pressure Hydrocephalus (NPH). Although a clear clinical triad has been defined, there are important differences in the clinical presentation and progression of this syndrome. This situation leads to an increase in the problems related to the diagnosis and treatment of NPH. In fact, although there have been remarkable developments in the field of medicine since NPH was first defined in 1964, the guidelines determining the diagnosis, management, and operation criteria of NPH were first prepared in 2004 to be implemented only in

Japan. Only in 2008 did Ishikawa et al. [4] produce worldwide applicable guidelines for its diagnosis and treatment. The information presented above is the most convincing evidence of the type of dynamic disease we are dealing with. On the other hand, due to reasons such as advancements in health, improved treatment options, increased education level, and conscientious diet, the share of the older population is constantly increasing. It is projected that as people's quality of life improves and their life expectancy rises, more old people would develop this condition. In the light of current information, it is predicted that 20% of the world population will be individuals over 65 years old by 2050. While the world's population has grown 4 times in the last 100 years (1950–2050), the fact that the elderly population will grow 10 times is a significant point that should be highlighted. In this case, it becomes even more important to age healthy and to keep the elderly population active. The most important task of neurologists, neurosurgeons, and psychiatrists in society is to provide early diagnosis and appropriate treatment of patients with NPH in society, especially given the socioeconomic consequences of this disease, particularly the burden of dementia on the individual, their families, and society. This is because it is emphasized that the earlier these patients are diagnosed and treated correctly, the more (most if not all) of the clinical symptoms are reversible.

2. Classification

NPH is divided into two groups as secondary NPH (sNPH) that develops due to decreased resorption of CSF due to inflammation and fibrosis at the arachnoid granulation level caused by subarachnoid hemorrhage, intraventricular hemorrhage, meningitis, or traumatic brain injury, and the second is the idiopathic NPH (iNPH) which does not have a causal disorder. A common feature of both diseases is that they do not contain any obstructions to the flow of CSF within the ventricular system of the brain. iNPH and sNPH do not differ in terms of prognosis. The sole significant clinical difference between them is that sNPH affects people of all ages, whereas iNPH often occurs more in the 60-70s [5, 6].

3. Incidence-prevalence

Epidemiological data on NPH are limited. Furthermore, due to the lack of uniform diagnostic criteria, reports on the incidence and prevalence of this disease, which has a wide clinical range, are partially inconsistent. The annual incidence of NPH is estimated to be between 0. 2 and 5.5 cases per 100,000 individuals. Its prevalence is reported to be 0.003% for persons under 65 years of age and 0. 2% to 2.9% for persons 65 years and older [7, 8]. In an epidemiological study conducted by Jaraj et al. [9], the probable prevalence of iNPH was found to be 0. 2% in people aged 70–79, and 5.9% in people aged 80 and older. Another recent epidemiological study also confirmed the inadequacy of incidence-prevalence reports of NPH [10]. Like other neurodegenerative diseases, the prevalence and incidence of NPH increases in direct proportion to age. In various studies, it was determined that there was no difference between males and females in terms of incidence [11–13].

4. Pathophysiology

It is important to clarify its pathophysiology for reliable diagnosis and treatment of NPH patients. Its pathophysiology is yet unknown, and it differs from other adult

hydrocephalus causes. In addition to the fact that pathological alterations change CSF pressure, it is also related to changes in CSF dynamics. The CSF circulation spaces in the brain parenchyma within a rigid cranium work as a dynamic system that continually seeks to adapt to new situations in order to keep the ICP constant. These structures give instantaneous responses to changes in CSF production-absorption, changes in arterial–venous flow to the brain, changes in the compliance of intracranial structures, and changes in intracranial pressure. This process is very important in terms of ensuring the correct functioning of the brain. Cerebral blood flow differs with heart rhythm. The arterial supply is pulsative, whereas the venous flow is non-pulsative, causing temporary rises in CSF pressure. In two ways, the system tries to compensate for this. First, vascular structures can reduce arterial blood flow by changing compliance. The second is that the outflow of CSF increases along the cerebral aqueduct. ICP is attempted to be kept constant thanks to these compensatory mechanisms. The decrease in arterial modulation is first compensated by increased pulsatile CSF flow. However, the progressive increase of the pulsatility amplitude causes large ICP pulsations that determine the "water-hammer" effect. These enhanced vibrations create venous damage in the periventricular region, and the process of pushing the brain against the skull continues to expand the ventricles, resulting in hydrocephalus. As a result, the compensatory mechanisms, that are activated in order to maintain the ICP stable, create pathological changes in neural tissue [14]. In fact, hydrocephalus can be defined as the expansion of the ventricles in response to the reduction of the subarachnoid space in the cerebral tissue. This situation is secondary to the increase in the pressure gradient between the ventricles and the subarachnoid space, known as the transmantle pressure [15]. It is still unclear what triggers the initial reduction in arterial compliance in this process. Ischemia emerging in the white matter surrounding arterioles could explain the insufficiency in autoregulation. The ventricular enlargement causes the arterioles and venules around the ventricle to compress and stretch over time, resulting in poor/insufficient cerebral perfusion [16–19]. Moreover, a strong relationship has been described between impaired cerebral blood flow and NPH. Therefore, clinically, the association of NPH with cerebrovascular disease is frequently encountered. Ischemic changes in cerebral tissue caused by decreased/insufficient perfusion were shown in Cranial MRI. These structural changes detected by neuro-radiological imaging have also been supported by neuropathological studies [20–23]. Vascular changes that occur as a natural consequence of aging in humans may be the triggering mechanism in the reduction of vascular compliance. This may explain the relationship between iNPH and vascular disease [24].

NPH also reduces compliance in large vascular structures such as the superior sagittal sinus [25, 26]. Increased transvenular resistance in the sagittal sinuses has been hypothesized as a factor in the onset of NPH. According to this viewpoint, CSF resorption will be affected by increased transvenular resistance [27, 28]. As a result, none of the proposed theories can adequately explain how NPH develops, what factors trigger it, or how structural alterations occur. Although these presented hypotheses appear to complement one other, the debates about pathogenesis continue.

5. Clinic

Symptoms in NPH have been defined as a "triad". However, having all of the symptoms at the same time is not necessary for diagnosis. The presence of two or more of the key symptoms (even a cardinal clinical symptom) such as apraxia of gait, dementia, and urinary incontinence, as well as bilateral dilatation of the ventricles, is necessary to diagnose the disease. The clinical signs and symptoms of this syndrome are highly diverse. Symptoms of this disease, which has an insidious

onset, appear gradually over a period of at least 6 months. The rate and extent of worsening of symptoms vary from one patient to another. Some patients and families are unaware of symptoms until a triggering event, such as surgery, occurs. Careful questioning can clarify the nature of symptom onset.

Decreased cerebral perfusion as a result of ventriculomegaly may be a reason for the classic symptoms of NPH. Neurological signs and symptoms, such as apraxia of walking, are thought to be caused by a combination of mechanical stretching of the periventricular fiber tracts, disruption of brain parenchyma tissue as a result of reduced cerebral blood flow, and periventricular edema [29–34]. Neuro-psychiatric symptoms have been suggested to be associated with brain regions such as the anterior cingulate cortex (ACC) and thalamus [35–37] because it has been determined that there is low perfusion in the anterior cingulate cortex and thalamus in NPH patients. Dysfunction in these regions is effective in the emergence of psychiatric symptoms. Therefore, increased/improved cerebral perfusion and oxygen metabolism from the frontal cortex and thalamus may cause neuropsychiatric and other symptoms in NPH patients after shunt surgery [38, 39]. There are publications reporting that psychiatric symptoms and syndromes occurring in the NPH clinic are related to changes in central neurotransmitter activity [40].

Although any of the main symptoms can present as the initial symptom in the NPH clinic, gait and balance disorders usually occur early and have a substantial impact on the individual's life. Dementia and urinary incontinence are symptoms that progress with the disease, albeit they usually appear at later stages of the disease [41].

6. Gait disorder

As described in many published series and guidelines, gait disturbance is the first clinical symptom that affects almost all patients. Dizziness is a common initial complaint among patients. The instability in NPH is better with the patient's eyes open, but patients still stand on a wide base even with their eyes open. When a patient's walking ability is compromised, it has a detrimental influence on their quality of life. At first, gait and balance disorders may appear to be mild. Patients initially complain of climbing and descending stairs, as well as getting up and sitting in a chair. Parallel to the progression of the disease, the patient's gait pattern deteriorates. Instead of the heel-to-toe gait cycle, which should normally be accomplished by raising the feet, these patients tend to slide their feet on the ground. This way of walking is described as "robotic", "sticky-footed" or "magnetic phenomenon" [42]. The disconnection between the basal ganglia and the frontal cortex during walking, as well as the co-contraction of opposing muscles, is suggested to be the source of this gait pattern, which is usually found in parkinsonism (bradykinetic, magnetic) [43, 44]. In the absence of primary sensorimotor deficits, these patients have a higher level of gait disturbance and impaired postural and locomotor reflexes [45]. Gait apraxia develops with the advent of cognitive disorders in the later stages of the disease, and individuals become unable to walk. If these patients are not diagnosed and treated early, they are eventually confined to a wheelchair.

Extrapyramidal symptoms may occur rarely in patients with NPH, but spasticity, hyperreflexia, and other upper motor neuron signs and lateralizing findings are not common. Since the symptoms are bilateral in NPH, lateralizing findings should alert the clinician to the presence of other neuropsychiatric disorders in the differential diagnosis. To assess diagnosis and prognosis, a standard gait assessment (e.g., Tinetti score, Boon Scale) should be performed both before and after the lumbar puncture (LP). The clinical finding with the highest probability of recovery (more than 85 percent) after shunt surgery is apraxia of walking, which is frequently the first main symptom of the disease [46–48].

7. Cognitive disorder

Cognitive deficit in NPH is basically of the "subcortical" type, which includes memory impairment, psychomotor retardation, and impaired ability to apply/use the acquired knowledge [49, 50]. These cognitive and behavioral disorders accompanying NPH are generally defined as "frontal-subcortical dementia or frontal-subcortical dysfunction" [51, 52]. This term is used to describe a pattern of mental decline marked by a lack of interest (apathy) in one's surroundings and oneself, as well as a lack of inner strength (amotivation) that drives one's activities and behaviors [53, 54]. For this reason, patients have difficulty in performing their daily living activities even at the onset of the disease. In this period, it is possible that an abnormality will not be identified in the psychometric tests that will be done on the patients.

Dementia is the most serious symptom in the clinical triad, as it has a negative impact on patients' work capacity as well as their social functioning. NPH is thought to be the etiological cause of 5% of dementia [55]. Even everyday activities like driving, shopping, and keeping track of appointments are challenging for these patients. There is no single type of dementia since dementia symptoms in NPH span a broad clinical spectrum. Instead, depending on the degree of permanent brain damage that has occurred, there are variable degrees of cognitive alteration. For this reason, it is not a very correct approach to define cognitive disorders that occur in NPH as dementia in the early period. Some patients have no clinical evidence of dementia, only mild or moderate cognitive deficits, and most of these patients respond well to shunt surgery [56, 57]. At least two of the following must be present for cognitive abnormalities in NPH patients to be defined as dementia.

- Psychomotor slowing.

- Attention impairment and concentration reduction.

- Short-term memory impairment (cannot repeat learned information).

- In the late phase of the disease, indifference/indifference to environmental stimuli, decreased desire to speak/not speaking at all, decreased thinking/ reasoning ability [58].

Since the Mini-Mental State Test and the DEMTEC Test were designed to evaluate cortical dementias, they are not appropriate for evaluating subcortical frontal lobe deficiencies (cognitive deficits) in NPH [59]. The Stroop test, digit span test, and Rey auditory-verbal learning test can be used instead. However, personality changes, anxiety, depression, psychotic syndromes such as delusions, hallucinations, and aggression may also be seen in NPH patients, as well as obsessive–compulsive disorder, Othello syndrome, and various other cognitive disorders such as theft, and mania [60–63]. Depression can be seen in the NPH clinic, although it is rare. In fact, only a tiny portion of these patients who show clinical signs of depression is really diagnosed with depression. Symptoms such as apathy and bradyphrenia that occur in NPH patients may mimic depression. Differential diagnosis between depression and NPH can be challenging as neuropsychological assessment profiles are similar [64, 65]. Therefore, before being diagnosed with depression, NPH patients should have a thorough psychiatric examination, and therapy should be started if actual depression is present. Again, delirium is not encountered in the NPH clinic, and its presence implies the existence of another disease or pharmacological side effect accompanying the disease [41]. Boon AJ et al. [66] reported that iNPH patients showed severe attention deficits. Although the

NPH clinic contains quite different and complex neuropsychiatric symptoms, the decision to have an early shunt surgery can continue to improve cognitive deficits in approximately 80% of patients with NPH, however, the presence of vascular dementia, Alzheimer's dementia, or comorbid diseases at the same time affects the success of surgical treatment negatively and reduces the recovery rate.

8. Urinary incontinence

Urinary symptoms in NPH may occur as urinary frequency, urgency, or incontinence. The bladder dysfunction of NPH is usually in the form of urinary urgency and this condition is almost always present [67, 68]. These patients have difficulty in preventing bladder emptying [69]. Patients have difficulties keeping urinary continence and may suffer urgency with a few drops of urine leakage before reaching the toilet, even though they are aware of the need to urinate at first. Therefore, nocturia is common in NPH patients. Incontinence or having wet clothes are not characteristic of NPH. True urinary incontinence develops later in the course of the disease. While patients initially suffer from increased urinary frequency, they then develop sudden incontinence and eventually persistent urinary incontinence. Bladder dysfunction is due to stretching of the periventricular nerve fibers and loss of subsequent inhibition (partial) of bladder contractions. Bladder function disorders in NPH are caused by detrusor overactivity due to a lack of central inhibitory control, which can be partial or complete [70]. It is extremely rare for fecal incontinence to occur as a symptom of NPH. Therefore, the presence of fecal incontinence in a patient with NPH should first raise suspicion of another type of neurodegenerative disease in the clinician. If a patient with NPH has fecal incontinence as one of the clinical indicators, it suggests he has severe frontal subcortical dysfunction.

When applied early, a CSF shunt can help about 80% of NPH patients with bladder dysfunction; however, if surgery is done at an advanced stage in the disease, as in other symptoms, the percentage would be no more than 50-60%.

9. Diagnosis

For diagnosis, the physical and neurological examinations, clinical symptoms, neuropsychological and neuroimaging findings should all be evaluated as a whole. For this purpose, the clinician should clearly demonstrate the presence of hydrocephalus and the absence of severe cortical atrophy. All patients with NPH should have enlarged ventricles. Although ventriculomegaly is detected in many neurodegenerative diseases and senile cerebral atrophy, these patients may not have any clinical signs of hydrocephalus. Hence, the terms hydrocephalus and ventriculomegaly are not synonymous. To summarize, not all elderly patients with large ventricles have NPH. Ventriculomegaly makes sense when accompanied by clinical symptoms.

Today, in most cases where neurological symptoms are new, Computerized Brain Tomography (CBT) is often used because it is quick and easy to obtain, or Magnetic Resonance Imaging (MRI) because it provides more detailed information about cerebral anatomy/pathology. Furthermore, high-speed and high-resolution MRI techniques can better define aqueductal stenosis, and MRI phase-contrast techniques show the hyperdynamic aqueductal CSF flow that has been associated with shunt-responsive NPH.

Radiological findings detected by MRI/CBT (**Figure 1**).

- Disproportionate ventricular enlargement to sulcal atrophy with typical rounding of frontal horns.

- Periventricular high-density and/or low-density areas (leukoaraiosis) seen diffusely/locally in the white matter due to the transependymal passage of CSF.

- Thinning and elevation of the corpus callosum [71].

- The Evans index, as determined by dilatation of the third and lateral ventricles without obstruction in the CSF circulation and by MRI or CT, should be at least 0. 3 [72].

- Flow gap in the aqueduct detected in spin-echo sequences and called hyper-dynamic aqueduct or jet sign (this should be confirmed by hyperdynamic aqueduct phase-contrast MRI) [73].
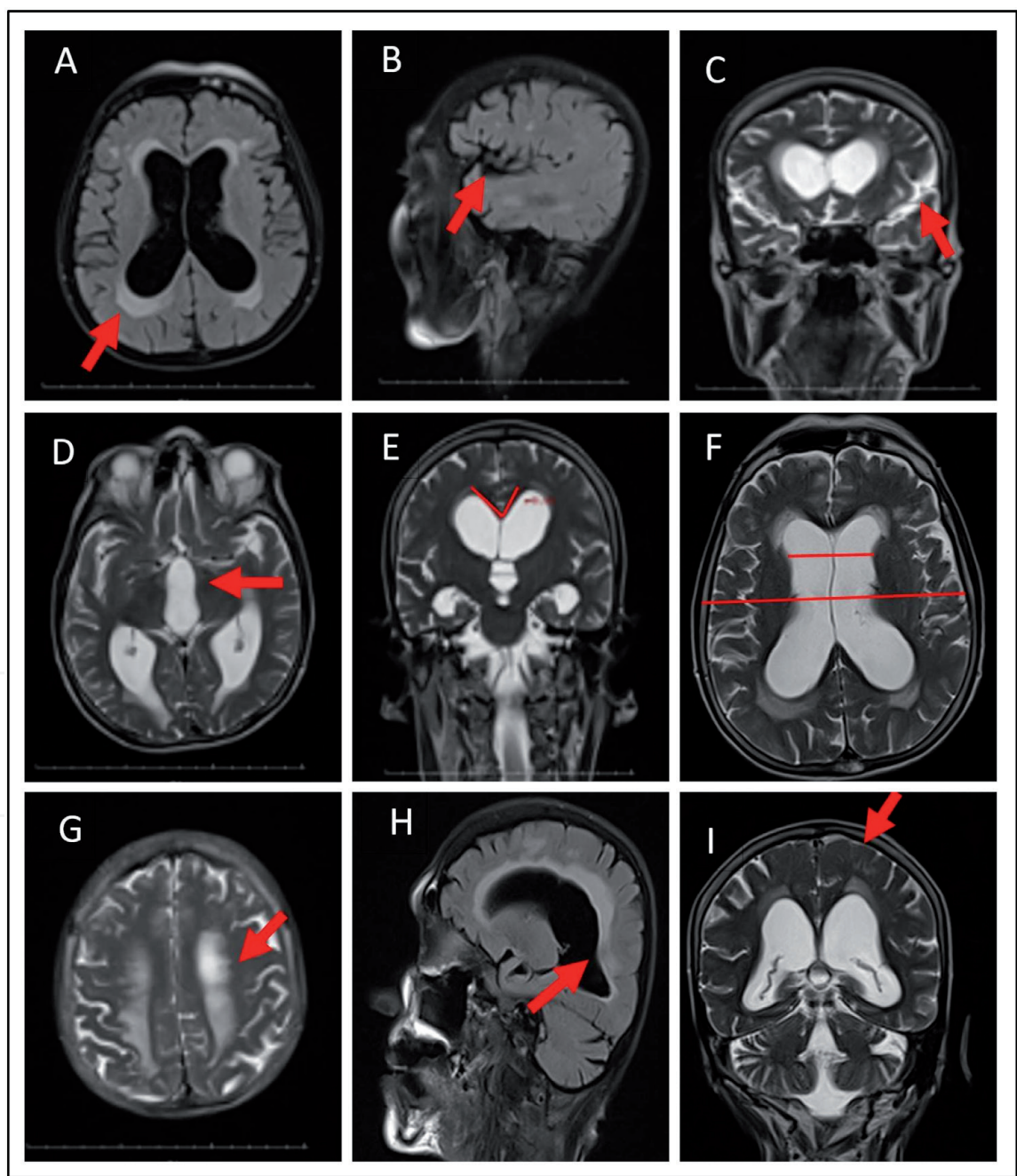
Figure 1.
MRI images of NPH a: Periventricular hyperintensity, B: Enlargement of Sylvian cistern (sagittal), C: Enlargement of Sylvian cistern (coronal), D: Dilatation in the third ventricle, E: Callosal angle, F: Evans index, G: Hyperintensity in white matter, H: Bulging on the roof of the ventricle, I: Effacement of sulci at midline vertex.

The presence of a narrow CSF area in high convexity/midline areas on radiological imaging, and disproportionately enlarged subarachnoid spaces particularly in the Sylvian fissure and basal cisterns, are termed 'Disproportionally Enlarged Subarachnoid Spaces Hydrocephalus' (DESH). This is an indirect sign that CSF flow between the basal cisterns and the arachnoid granulations is being blocked. The existence of this symptom is thought to be the most sensitive indicator for shunt surgery, while its absence indicates brain atrophy [74]. So far, no characteristic neuropathological lesion of NPH has been detected [75–77].

Neuroimaging tests are necessary but not sufficient to diagnose NPH. Invasive tests such as lumbar puncture (LP). and External Lumbar Drainage (ELD) are needed in addition to non-invasive procedures like radiological imaging to improve diagnostic and prognostic accuracy in these patients. Both International and Japanese guidelines recommend diagnostic LP and/or ELD to all patients with suspected NPH. While there is a response to CSF intake in the presence of NPH, there is no response to CSF intake in the absence or minimal level of NPH. CSF drainage also has predictive value for shunt surgery. Patients whose symptoms are relieved by CSF drainage are expected to respond positively to shunt surgery as well. With LP taking 30–50 mL of CSF, changes in gait and cognitive functions are expected after 30 minutes to 4 hours (rarely a few days). If there is a positive response to the tap test, shunt surgery may be recommended, but failure to respond does not exclude the shunt response, because even in patients with normal CSF pressure in the LP, recovery was observed in approximately 50% of them following shunt surgery [78–82]. ELD may be considered in patients who do not respond to the Tap test but are still clinically suspected of having NPH. With ELD, controlled CSF drainage of approximately 10 mL/h for 2–3 days or 150 to 200 mL per day for 2 to 7 days is performed. The patient's gait and neuropsychological tests are recorded daily before the procedure, during CSF drainage, and after catheter removal.

It is difficult to explain the detection of CSF pressure at normal levels in NPH dynamics. Although normal CSF pressure can be detected with a single LP, in fact, 24-hour monitoring might occasionally reveal abnormally high pressures or consistently high/normal pressures. Although CSF pressure has been found to be normal in a single LP, there is a consensus that episodes of increased CSF pressure occur in NPH. For the development of iNPH or sNPH, it is predicted that the baseline ICP is high, at least during the disease stages, and that this high pressure decreases with dilatation of the ventricles. Long-term intracranial pressure (ICP) measurements, such as those taken by some centers for 24 to 72 hours, are not advised for routine usage, both because their predictive values have not yet been adequately documented and because they necessitate specialized equipment and expertise.

10. Differential diagnosis

Regression in motor and cognitive functions, as well as urine incontinence, are common with aging. The addition of other neurodegenerative diseases, such as those that increase with age, and some surgery (cervical/lumbar spinal stenosis) and internal diseases (hypothyroidism, vitamin B12 deficiency) make the differential diagnosis difficult. It may not be easy to distinguish Alzheimer's disease (AD) and Parkinson's disease, which exhibit similar clinical symptoms such as gait disturbance and dementia, from NPH. Also, having vascular or Alzheimer's dementia simultaneously in three-quarters (75%) of their patients with NPH makes the situation even more complicated. On the other hand, because each of the cardinal symptoms of NPH has a variety of etiologies, it might mimic a variety

of neurodegenerative diseases. Patients with isolated NPH are extremely uncommon in clinical practice due to the numerous comorbidities that often accompany the symptoms of NPH. The clinical triad peculiar to this disease is actually non-classical, as similar symptoms can be found in a variety of disorders. Therefore, a comprehensive differential diagnosis table ranging from psychiatric disorders to neurological diseases should be considered when distinguishing NPH from other diseases in elderly patients. The differential diagnosis of gait disorders includes peripheral neuropathy, inner ear disorders, spinal cord diseases, alcohol use, and deficiencies of vitamins such as B6 and B12. Clinical and neuroimaging data are very important in the differential diagnosis. Early and accurate determination of the differential diagnosis will save both the clinician and the patient from a series of invasive and noninvasive tests.

Findings that make a diagnosis of NPH less likely include the following:

- ICP: Above 25 cm H_2O.

- AGE: Patients younger than 40 years old.

- SYMPTOM: Asymmetrical or transient symptoms.

- CORTICAL DYSFUNCTION: Having deficits such as aphasia, paresis.

- DEMENTIA: The absence of gait disturbance accompanying the dementia clinic.

- CLINICAL PROCESS: No progression of symptoms.

Some of the diseases frequently encountered in the differential diagnosis are Alzheimer's disease (AD) and Parkinson's disease. Similar to Parkinson's disease, episodes of hesitation and freezing may occur in the gait of NPH patients. However, resting tremors and the typically unilateral symptoms of Parkinson's disease are uncommon in NPH. NPH patients' failure to respond to anti-parkinsonian medicines may also help with diagnosis.

The subject AD, another common disease in differential diagnosis, is quite complex and difficult. AD is thought to account for 50–60% of all dementias in the elderly [83–85]. It is not always possible to distinguish between patients with NPH and those with AD based solely on their medical history and physical examination. Thanks to data gained from MRI and neuropsychological tests, distinguishing AD from NPH is now easier than in past years. The mental disorder in NPH is a subcortical type. While the severity of cognitive impairment is mild or moderate in patients with NPH, mental disorders in AD patients are both the first symptom and advanced. Again, dementia signs occur with more severe symptoms in AD than in NPH. This condition was confirmed by the presence of hippocampal atrophy on CT or MRI [86–89]. Again, motor symptoms such as gait disturbance are rare in AD. In AD, long-term, short-term, and sensory memories are all impaired, while in NPH memory is partially preserved. In NPH, brain dysfunction mainly arises in the frontal cortex, whereas in AD, the major dysfunction originates from the medial temporal lobe, thus, medial temporal lobe atrophy on MRI suggests AD [90]. On the other hand, when considering the response to shunt surgery, it is critical to distinguish these two diseases, which overlap in terms of clinical symptoms. From this standpoint, many studies have investigated biomarkers in CSF to both improve diagnosis and predict shunt efficacy. The specific combination of low Aβ-42 and increased P-tau detected in the CSF has actually been accepted as the biological

signature of AD [91]. In contrast, Graff-Radford [92] reported that CSF markers are not useful in distinguishing between the NPH patients from the patients with comorbid AD. Complete blood count, biochemical profile, neuropsychological tests, MRI of the cervical, thoracic or lumbar spine in addition to cranial MRI, electromyography/nerve conduction velocity study and urology consultation can be performed to comprehensively evaluate the differential diagnosis.

11. Treatment

Although NPH is a clinically well-known disease, the indications for shunt surgery and the estimation of surgical outcomes are not clear. Although many devoted articles have been published to identify the most suitable candidates for surgical treatment, there is still no consensus on who is the best candidate for surgery and how to select these patients. Reliable indications of good surgical response are still lacking, particularly with regard to the shunt procedure. In the presence of short history, a known cause of hydrocephalus, predominance of gait disturbances, and CT or MRI findings for hydrodynamic hydrocephalus, it is not difficult to decide on surgery and recommend a shunt to the patient. Today, identifying patients with NPH and applying effective treatment methods still pose challenges for neurosurgeons. However, despite all these difficulties, if diagnosed and treated early, the unusual appearance of these symptoms affecting elderly individuals can be prevented and significant improvements in their life quality can be achieved.

Advanced diagnostic and therapeutic methods and clinical successes have shown that surgical treatment for NPH is superior to conservative treatment. Even if one or two main symptoms are present, NPH should be diagnosed and treated, as waiting for the clinical triad to occur for diagnosis can drastically diminish the response to shunt surgery. This is because the longer NPH patients go without treatment, the worse their prognosis becomes and the shorter their life expectancy becomes.

Using a catheter to alter the flow path of CSF is now the recognized therapeutic procedure all around the world. Shunt surgery is indicated for patients who respond to CSF drainage or who have CSF hydrodynamic variables consistent with NPH [75, 93–95].

However, it is crucial to identify other diseases that mimic NPH before deciding on surgical treatment as it will directly affect the quality of life of patients. There is no evidence that the time spent identifying and treating these disorders in the differential diagnosis lowers the chances of response to shunt surgery. The most essential component that promotes surgical success is a more thorough evaluation performed without haste. Moreover, it should be noted that not all patients with NPH are candidates for shunt surgery. For each patient, the benefit–risk ratio should be assessed separately. Before the surgical operation, possible complications of shunt surgery (infection, embolization, shunt failure, subdural hematoma, and effusion) should be considered and patients should be informed about the surgical risks as well as the potential benefit. Patients should be informed about the problems they will encounter in their daily lives (such as gait disturbance, dementia, incontinence) and potential complications of shunt surgery if they are not operated on. Providing information on the following issues prior to surgical consent will improve the patient's and their relatives' compliance with post-surgery treatment.

a. After surgical treatment, iNPH has a potential cure rate of 30-50% and sNPH of 50-70%.

b. The least reversible symptom with surgical treatment is dementia.

   c. The complication rate of surgical treatment varies between 20% and 40%, but serious complications do not exceed 5-8%.

The passage of CSF from one compartment to another by bypassing the natural flow pathways with the aid of a catheter remains the main treatment method for NPH. This shunt procedure is based on the notion that it will minimize the elevated transmantle pressure caused by ventriculomegaly, therefore relieving the symptoms associated with NPH [14]. Today, ventriculoperitoneal (VP) shunts are the most commonly used ones for this purpose. Shunt valves and configuration are dependent on surgeon experience and patient preference. There is no objective evidence that one type of shunt is superior to another. Low-pressure shunts were frequently employed in the past, and the clinical response was better. However, because complications including excessive drainage and subdural hematoma are more common with these shunts, they have been phased out except in rare circumstances. Today, medium pressure shunts or adjustable shunts are more preferred. Adjustable shunts have the advantage of allowing the pressure setting to be gradually lowered or raised until the patient's symptoms improve. In this way, complications that may arise as a result of under or excess drainage can be avoided by changing the pressure without surgery. Another advantage is that it can be administered safely in patients who are on anticoagulation therapy for cardiac or neurological disorders [96].

In Japan, patients with iNPH are mainly treated with lumbar peritoneal shunts. In recent years, this surgical procedure has been widely used all over the world. In terms of effectiveness, one type of shunt has no superiority over the other. However, although the complication rate associated with the device itself is higher in lumbar peritoneal shunts than in ventriculoperitoneal shunts, the fact that lumbar peritoneal shunts are minimally invasive, do not have the fatal complications seen in ventriculoperitoneal shunts, and are more economical has allowed them to be a step forward in treatment [97]. Endoscopic third ventriculostomy has not been proven to be effective in the treatment of iNPH. In patients who are debilitated and shunt surgery is contraindicated, serial lumbar punctures are not recommended as an alternate treatment, except for a limited period of time.

Although it is difficult to draw definitive conclusions, three decades of publications on NPH and surgical experience have summarized the factors that can help predict post-shunt outcomes as follows [98].

   a. Factors predicting a good surgical outcome.

- Clinical gait disturbances appearing before cognitive deficits.

- Short duration of mental deterioration history.

- Mild or moderate level of mental disorder.

- Presence of hydrocephalus with known etiology such as subarachnoid hemorrhage, meningitis.

- Detection of significant improvement in clinical findings after CSF drainage.

- Occurrence of 50% or more B waves in continuous intracranial pressure monitoring.

- Absence of significant white matter lesions on MRI.

b. Factors predicting poor surgical outcomes.

- Dementia being the first symptom among clinical findings.

- Detection of clinical signs of severe dementia.

- Detection of significant cerebral atrophy or diffuse white matter involvement on MRI.

Although some studies have indicated a high success (recovery) rate of roughly 80-90% in the improvement of clinical symptoms following surgery [99, 100], the overall rate has been reported to be 65-70% for sNPH cases and 30-50% for iNPH cases [50, 82, 101]. This discrepancy in surgical outcomes could be attributed to the presence of other NPH-related neurodegenerative and/or cerebrovascular disorders. Therefore, meticulousness in differential diagnosis and early treatment of comorbidities can eliminate this inconsistency.

However, the reasons why patients treated with shunts do not respond to shunt surgery are not fully understood. Before concluding that the surgical treatment was unsuccessful, it should be suspected that the failure was due to candidate selection or that the shunt was ineffective in cases where the desired clinical improvement was not achieved after surgery, particularly in patients whose ventricular size did not decrease after shunt or in those who only experienced temporary improvement after surgery [102].

Acknowledgements

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References

[1] Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci. 1965; 2: 307-327

[2] Hakim S, Venegas JG, Burton JD. The physics of the cranial cavity, hydrocephalus and normal pressure hydrocephalus: mechanical interpretation and mathematical model. Surg Neurol. 1976; 5: 187-210

[3] Adams RD. Fisher CM, Hakim S. et al. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. A treatable syndrome. N Engl J Med. 1965; 273: 117-126

[4] Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miyake H, Wachi A, Takeuchi T, Kazui H, Koyama H. Guidelines for management of idiopathic normal pressure hydrocephalus. Neurologia Medico-Chirurgica. 2008;48 (Suppl):1-23

[5] Torkelson RD, Leibrock LG, Gustavson JL, Sundell RR. Neurological and neuropsychological effects of cerebrospinal fluid shunting in children with assumed arrested "normal pressure" pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 1985;48: 799-806

[6] Bret P, Chazal J. Chronic ("normal pressure") hydrocephalus in childhood and adolescence. A review of 16 cases and reappraisal of the syndrome. Childs Nerv Syst. 1995; 11:687-691

[7] Brean A, Eide PK. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. Acta Neurol Scand. 2008; 118:48-53.

[8] Hiraoka K, Meguro K, Mori E. Prevalence of idiopathic normal-pressure hydrocephalus in the elderly population of a Japanese rural community. Neurol Med Chir. 2008; 48: 197-199

[9] Jaraj D, Rabiei K, Marlow T. et al. Prevalence of idiopathic normal-pressure hydrocephalus. Neurology. 2014; 82:1449-1454.

[10] Martin-Laez R, Caballero-Arzapalo H, Lopez-Menendez LA, Arango-Lasprilla JC, Vázquez-Barquero A. Epidemiology of idiopathic normal pressure hydrocephalus: A systematic review of the literature. World Neurosurgery. 2015;87:298-310.

[11] Brean A, Fredo HL, Sollid S, Muller T, Sundstrom T, Eide PK. Five- year incidence of surgery for idiopathic normal pressure hydrocephalus in Norway. Acta Neurol Scand. 2009; 120: 314-316

[12] Tanaka N, Yamaguchi S, Ishikawa H, Ishii H, Meguro K. Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: the Osaki-Tajiri project. Neuro-epidemiology 2009; 32: 171-175.

[13] Krauss JK, Halve B: Normal pressure hydrocephalus: surveyon contemporary diagnostic algorithms and therapeutic decision making in clinical practice. Acta Neurochir. 2004; 146: 379-388.

[14] Gooriah R, Raman A. Idiopathic normal pressure hydrocephalus: An overview of pathophysiology. Clinical Features, Diagnosis and Treatment. 2016. DOI: 10.5772/64198

[15] Greitz D, Greitz T, Hindmarsh T. A new view on the CSF-circulation with the potential for pharmacological treatment of childhood hydrocephalus. Acta Paediatrica. 1997;86:125-132

[16] Bradley WG. Normal pressure hydrocephalus: New conceptson etiology and diagnosis. AJNR. American Journal of Neuroradiology. 2000; 21:1586-1590

[17] Greitz T. Effect of brain distension on cerebral circulation. Lancet. 1969; 2: 863-865

[18] Sato O, Ohya M, Nojiri K, Tsugane R. Microcirculatory changes in experimental hydrocephalus: morphological and physiological studies. In: Shapiro K,Marmarou A, Portnoy H (eds) Hydrocephalus. Raven, 1984; 215-230

[19] Del Bigio MR, Bruni JE Changes in periventricularvasculature of rabbit brain following induction of hydrocephalu sand after shunting. J Neurosurg. 1988; 69:115-120

[20] Krauss JK, Droste DW, Vach W, Regel JP, Orszagh M,Borremans JJ, Tietz A, Seeger W. Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: Effectof periventricular and deep white matter lesions. Neurosurgery. 1996;39(2):292-300

[21] Tullberg M, Jensen C, Ekholm S, Wikkelsø C. Normal pressure hydrocephalus: Vascular white matter changes on MR images must not exclude patients from shunt surgery. Am J Neuroradiol. 2001;22(9):1665-1673

[22] Akai K, Uchigasaki S, Tanaka U, Komatsu A. Normal pressure hydrocephalus. Neuro-pathological study. Acta Pathologica Japonica. 1987;37(1):97-110

[23] Del Bigio MR. Neuropathological changes caused by hydrocephalus. Acta Neuropathologica. 1993;85(6):573-585

[24] Grünewald RA. Normal pressure hydrocephalus: Pathophysiology. Practical Neurology. 2006;6:264-266

[25] Mase M, Yamada K, Banno T, Miyachi T, Ohara S, Matsumoto T. Quantitative analysis of CSF flow dynamics using MRI in normal pressure hydrocephalus. Acta Neurochirurgica. Supplement. 1998;71:350-353

[26] Bateman GA. Vascular compliance in normal pressure hydrocephalus. Am J Neuroradiol. 2000;21(9):1574-1585

[27] Castro ME, Portnoy HD, Maesaka J. Elevated cortical venous pressure in hydrocephalus. Neurosurgery. 1991;29:232-238

[28] Portnoy HD, Branch C, Castro ME. The relationship of intracranial venous pressure to hydrocephalus. Child's Nervous System. 1994;10:29-35

[29] Oliveira MF, Pinto FCG, Nishikuni K, Botelho RV, Lima AM, Rotta JM. Revisiting hydrocephalus as a model to study brain resilience. Front Hum Neurosci. 2011;5:181.

[30] Greitz TVB, Grepe AOL, Kalmer MSC. Pre- and post-operative evaluation of cerebral blood flow in low pressure hydrocephalus. J Neurosurg. 196931:644-51.

[31] Fisher CM. Hydrocephalus as a cause of gait disturbances in the elderly. Neurology. 1982;32: 1258-1263.

[32] Grubb RL, Raichle ME, Gado MH, Eichling JO, Hughes CP. Cerebral blood flow oxygen utilisation and blood volume in dementia. Neurology. 1977;27:905-910

[33] Meyer JS, Kitagawa Y, Tanahashi N, et al. Pathogenesis of normal pressure hydrocephalus preliminary. Surg Neurol. 1985; 23(2): 121-133

[34] Mathew NT, Meyer JS, Hartmann A, Ott EO. Abnormal cerebrospinalfluid-blood flow dynamics. Implications in diagnosis, treatnent andprognosis in normal pressure hydrocephalus. Arc Neurol. 1975;32:657-664

[35] Craig AH, Cummings JL, Fairbanks L, Itti L, Miller BL, Liand J, Mena I. Cerebral blood flow correlates of apathy in Alzheimer disease, Archives of Neurology. 1996;53: 1116-1120.

[36] Lanctot KL, Moosa S, Herrmann N, Leibovitch FS, Rothenburg L, Cotter A, Black SE, A SPECT study of apathyin Alzheimer's disease, Dementia and Geriatric Cognitive Disorders. 2007;24: 65-72.

[37] Marshall GA, Monserratt L, Harwood D, Mandelkern M. Cummings JL, Sultzer DL. Positron emission tomography metabolic correlates of apathy in Alzheimer disease, Archives of Neurology. 2007;64 :1015-1020

[38] J. Miyamoto, K. Tatsuzawa, Y. Inoue, Y. Imahori and K.Mineura, Oxygen metabolism changes in patients with idiopathic normal pressure hydrocephalus before and after shunting operation, Acta Neurologica Scandinavica. 2007 116137-116143

[39] Tullberg M, Hellstrom P, Piechnik SK, Starmark JE, Wikkelso C. Impaired wakefulness is associated with reduced anterior cingulate CBF in patients with normal pressure hydrocephalus, Acta Neurologica Scandinavica. 2004;110:322-330

[40] Markianos M, Lafazanos S, Koutsis G, Sfagos C, Seretis A. CSF neurotransmitter metabolites and neuropsychiatric symptomatology inpatients with normal pressure hydrocephalus. Clin Neurol Neurosurg. 2009;111:231-234

[41] Williams MA, Relkin NR. Diagnosis and management of idiopathic normal-pressure hydrocephalus. Neurology Clinical Practice. 2013;3:375-385.

[42] Haan J, Jansen ENH, Oostrom J, Roos RAC Falling spells in normal pressure hydrocephalus: A favourable prognostic sign? Eur Neurol. 1987; 27:216-220

[43] Estanol BV Gait apraxia in communicating hydrocephalus. J Neurol Neurosurg Psychiatry. 1981 ;44: 305-308

[44] Knutsson E, Lying-Tunell U. Gait apraxia in normal-pressure hydrocephalus: patterns of movement and muscle activation. Neurology. 1985; 35: 155-160

[45] Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. Neurology. 1993;43:268-279.

[46] Fisher CM (1982) Hydrocephalus as a cause of disturbances of gait inthe elderly. Neurology 32:1358-1363

[47] Sørensen PS, Jansen EC, Gjerris F. Motor disturbances in normal pressure hydrocephalus. Special reference to stance and gait. ArchNeurol. 1986;43:34-38

[48] Graff-Radford NR, Godersky JC. Normal-pressure hydrocephalus. Onset of gait abnormality before dementia predicts good surgical outcome. Arch Neurol. 1986; 43:940-942.

[49] Thomsen AM, Børgesen SE, Bruhn P, Gjerris F. Prognosis of dementia in normal-pressure hydrocephalus after a shunt operation. Ann Neurol. 1986; 20:304-310

[50] Cummings JL, Benson DF Hydrocephalic dementia. In:Dementia: a clinical approach, 2nd edn. Butterworth Heinemann, Boston. 1992:267-291

[51] Ogino A, Kazui H, Miyoshi N, Hashimoto M, Ohkawa S, Tokunaga H,Ikejiri Y, Takeda M. Cognitive impairment in patients with idiopathic normal pressure hydrocephalus Dementia and Geriatric Cognitive Disorders. 2006;21(2):113-119

[52] Tarnaris A, Toma AK, Pullen E, Chapman MD, Petzold A, CipolottiL, Kitchen ND, Keir G, Lemieux L, Watkins LD. Cognitive, biochemical,and imaging profile of patients suffering from idiopathic normal pressure hydrocephalus. Alzheimer's & Dementia. 2011;7(5):501-508.

[53] Larsson A, Wikkelsö C, Bilting M, Stephensen H. Clinical parametersin 74 consecutive patients shunt operated for normal pressure hydrocephalus. Acta Neurologica Scandinavica. 1991;84(6):475-482.

[54] Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. The Journal of Neuropsychiatry and Clinical Neurosciences. 1994;6(4):358-370.

[55] Vanneste JA. Diagnosis and management of normal-pressure hydrocephalus, J Neurol. 2000;247: 5-14.

[56] Fisher CM. Hydrocephalus as a cause of disturbances of gait in the elderly. Neurology. 1982:32:1358-1363

[57] Gerloff C, Pickard JD Normal pressure hydrocephalus. In:Brandt T, Caplan LR, Dichgans J, Diener HC, Kennard C (eds) Neurological disorders– course and treatment. Academic, San Diego. 1996:773-778

[58] Michael K, Andreas U. The Differential Diagnosis and Treatment of Normal-Pressure Hydrocephalus. | Dtsch Arztebl Int 2012; 109 (1-2):15-26

[59] Hellstrom P, Edsbagge M, Blomsterwall E, et al.: Neuropsychological effects of shunt treatment in idiopathic normal pressure hydrocephalus. Neurosurgery. 2008; 63: 527-535.

[60] McIntyre AW, Emsley RA. Shoplifting associated with normal pressure hydrocephalus: report of a case. J Geriatr Psychiatry. Neurol. 1990;3:229-230.

[61] Kwentus JA, Hart RP. Normal pressure hydrocephalus presenting as mania. J Nerv Ment Dis. 1987;175: 500-502.

[62] Bloom KK, Kraft WA. Paranoia - an unusual presentation of hydrocephalus. Am J Phys Med Rehabil. 1998;77:157-159.

[63] Yusim A, Anbarasan D, Bernstein C, et al. Normal pressure hydrocephalus presenting as Othello syndrome: case presentation and review of the literature. Am J Psychiatry 2008;165: 1119-1125.

[64] Rosen H, Swigar ME Depression and normal pressure hydrocephalus.A dilemma in neuropsychiatric differential diagnosis. J Nerv Ment Dis. 1976;163:35-40

[65] Hart RP, Kwentus JA. Psychomotor slowing and subcortical type dysfunction in depression. J Neurol Neurosurg Psychiatry. 1987;50: 1263-1266

[66] Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, Avezaat CJ, de Jong DA, Gooskens RH, Hermans J. Dutch normal pressure hydrocephalus study: Prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. Journal of Neurosurgery. 1997;87:687-693.

[67] Fisher CM Hydrocephalus as a cause of disturbances of gait in the elderly. Neurology 1982;32:1358-1363

[68] Bret P, Chazal J (L'hydrocéphalie chronique de l'adulte.Neurochirurgie. 1990 ; 36 [Suppl] :1-159

[69] Sakakibara R, Kanda T, Sekido T, et al. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. Neurourol Urodyn 2008;27:507-510

[70] Sakakibara R, Uchiyama T, Kanda T, Uchida Y, Kishi M, Hattori T. Urinary dysfunction in idiopathic normal pressure hydrocephalus. Brain and Nerve. 2008;60(3):233-239

[71] Ishii K, Kanda T, Harada A, Miyamoto N, Kawaguchi T, Shimada K,Ohkawa S, Uemura T, Yoshikawa T, Mori E. Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. European Radiology. 2008;18(11):2678-2683.

[72] Gyldensted C. Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. Neuroradiology.1977;14(4):183-192

[73] Bradley WG Jr. CSF flow in the brain in the context of normal pressure hydrocephalus. American Journal of Neuroradiology.2015;36(5):831-838.

[74] Sasaki M, Honda S, Yuasa T, Iwamura A, Shibata E, Ohba H. Narrow CSF space at high convexity and high midline areas in idiopathic normal pressure hydrocephalus detected by axial and coronal MRI. Neuroradiology. 2008;50(2):117-122

[75] Mori E, Ishikawa M, Kato T, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition.Neurol Med Chir 2012;52:775-809

[76] Hashimoto M, Ishikawa M, Mori E, Kuwana N. Study of INPH on neurological improvement (SINPHONI): diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-basedscheme: a prospective cohort study. Cerebrospinal Fluid Res. 2010;7:18.

[77] Williams MA, Malm J (2016) Diagnosis and Treathent of Idiopathic Normal Pressure Hydrocephalus. Continuum (Minneap Minn) 22:579-599

[78] Greenberg JO, Shenkin HA, Adam R(1977) Idiopathic normal pressure hydrocephalus- a report of 73 patients. J Neurol Neurosurg Psychiatry. 40:336-341.

[79] Black PMcL Idiopathic normal-pressure hydrocephalus. Results of shunting in 62 patients. J Neurosurg. 1980:53:371-377

[80] Pickard JD (1984) Normal pressure hydrocephalus – to shunt or not to shunt. In: Warlow C, Garfield J (eds) Dilemmas in the management of the neurological patient. Churchill Livingstone, Edinburgh, pp. 207-214

[81] Petersen RC, Mokri B, Laws ER . Surgical treatment of idiopathic hydrocephalus in elderly patients. Neurology. 1985; 35:307-311

[82] Vanneste JAL. Three decades of normal pressure hydrocephalus: are we wiser now? J Neurol Neurosurg Psychiatry. 1994; 57:1021-1025

[83] Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. Neurology. 1994; 44: 1593-1599

[84] Ichinowatari N, Tatsunuma T, Makiya H. Epidemiological study of old age mental disorders in the two rural areas of Japan. Jpn J Psychiatry Neurol. 1987;41: 629-636

[85] Sulkava R, WikstroÈm J, Aromaa A, Rautsalo R, Lehtinen V, LahtelaK, Palo J. Prevalence of severe dementia in Finland. Neurology 1985; 35: 1025-1029

[86] Golomb J, de Leon MJ, George AE et al (Hippocampal atrophy in normal pressure hydrocephalus is associated with severity of cognitive impairment. Neurology. 1993;43 [Suppl] 2: 211-212

[87] George AE, de Leon MJ, Miller J, Kluger A, Smith DC CT diagnostic

features of Alzheimer's disease: importance in the choroidal/hippocampal fissure complex. Am J Neuroradiol. 1990;11:101-107

[88] Golomb J, de Leon MJ, George AE, Kluger A, Convit A, Rusinek H,de Santi S, Litt A, Foo SH, Ferris SH. Hippocampal atrophy correlates with severe cognitive impairment in elderly patients with suspected normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 1994; 57:590-593

[89] Holodny AI, Waxman R, George AE, Rusinek H, Kalnin AJ, de Leon M. MR differential diagnosis of normal-pressure hydrocephalus and Alzheimer disease: significance of peri-hippocampal features. Am J Neuroradiol. 1998;19:813-819

[90] Jack CR Jr, Petersen RC, Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer disease. Neurology 1992;42(1):183-188.

[91] Blennow K, Hampel H CSF markers for incipient Alzheimer'sdisease. Lancet Neurol. 2003; 2:605-613.

[92] Graff-Radford NR. Alzheimer CSF biomarkers may be misleading innormal-pressure hydrocephalus. Neurology. 2014;83(17):1573-1575

[93] Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus: INPH Guidelines, part II. Neurosurgery. 2005;57:4-16.

[94] Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus: INPH Guidelines, part III. Neurosurgery. 2005;57:17-28.

[95] Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N.Surgical management of idiopathic

normal-pressure hydrocephalus: INPH Guidelines, part IV. Neurosurgery. 2005;57:29-39.

[96] Goodwin CR, Kharkar S, Wang P, Pujari S, Rigamonti D,Williams MA. Evaluation and treatment of patients with suspected normal pressure hydrocephalus on long term warfarin anticoagulation therapy Neurosurgery. 2007;60:497-501.

[97] Nakajima M, Miyajima M, Ogino I, Sugano H, AkibaC, Domon N, Karagiozov KL, Arai H. Use of external lumbar cerebrospinal fluid drainage and lumboperitoneal shunts with strata NSC valves in idiopathic normal pressure hydrocephalus: A single-center experience. World Neurosurgery. 2015;83(3):387-393.

[98] Klinge P, Hellström P, Tans J, Wikkelsø C. European iNPH multicenter study group. One-year outcome in the European multicentre study on iNPH. Acta Neurologica Scandinavica. 2012;126(3):145-153.

[99] Vanneste JAL. Diagnosis and management of normal-pressure hydrocephalus. Neurol. 2000;247:5-14

[100] Black PML, Ojemann RG, Tzouras A (1985) CSF shunts for dementia, incontinence, and gait disturbance. Clin Neurosurg 32:632-651

[101] Poca MA, Solana E, Martínez-Ricarte FR, Romero M, Gándara D,Sahuquillo J. Idiopathic normal pressure: Results of a prospective cohort of 236 shunted patients. Acta Neurochirurgica. Supplement. 2012;114:247-253.

[102] Williams MA, Razumovsky AY, Hanley DF. Evaluation of shunt function in patients who are never better, or better then worse after shunt surgery for NPH. Acta Neurochir. 1998;71:368-370