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VARIA

Normal pressure hydrocephalus – Diagnosis and therapeutic challenges

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Abstract: *Normal pressure hydrocephalus (NPH) is a rare pathological condition that generally affects older people (>65 years old), and can take one of two forms: idiopathic or secondary. It is a reversible cause of dementia, and it manifests itself through a very specific triad: gait impairment, urinary incontinence, and dementia. The clinical diagnosis of NPH is particularly difficult to establish due to the association between these symptoms and old age, as well as due to the absence of specific paraclinical markers. Nevertheless, a holistic application of clinical, imagistic, paraclinical criteria, as well as of the various developed scales may, in time, lead to a diagnosis. Moreover, the evolution of magnetic resonance imaging has certainly made easier to establish the condition. The sole therapeutic method proven to be efficient is shunting surgery which has good results in the majority of the cases, showing clear signs of improvement from the very first-day post-surgery.*

Keywords: *normal pressure hydrocephalus, ventriculoperitoneal shunt, aqueductal stenosis, cerebral ventriculomegaly, communicating hydrocephalus, obstructive hydrocephalus*

INTRODUCTION

Normal pressure hydrocephalus (NPH) was firstly recognized by Adams et al. in 1965, by identifying a number of patients suffering from hydrocephalus, but having a normal pressure in the cerebrospinal fluid (CSF) at the lumbar puncture (LP) [1]. This represented a potentially reversible syndrome. The pathology is most often present in older people, and it manifests itself through a gait disturbance, urinary incontinence, and cognitive deficit. It has also been determined that gait impairment, along with one other characteristic element is essential for diagnosis. The clinical assessment demands further examinations, such as brain imagery or draining the CSF, to properly confirm the condition [2].

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Traditionally, hydrocephalus was divided into two types: communicating hydrocephalus or obstructive hydrocephalus (non-communicating). The former type is characterized by an increase in the volume of CSF without any stenotic lesions in the drainage. In this case, the classification of NPH is still the one being used since 1965: idiopathic NPH (iNPH) – in roughly 50% of all cases, and secondary NPH (sNPH), which comes as a result of either subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), meningitis, intracranial tumors or trauma [1]. While iNPH is generally noticed at adults, sNPH may be present at any age, with both genders being affected equally [3]. Apart from the ventriculomegaly, there are no other observable radiological signs.

Obstructive or non-communicating hydrocephalus comes after the stenosis of the drainage between ventricles and the subarachnoid space, either congenital or acquired. The stenosis of the cerebral aqueduct is a common cause in young adults, although the symptoms are not visible until

adulthood [4].

In the largest study ever conducted on NPH, in Sweden, the results estimated a 0.2% prevalence in the 70-79 age group, and 5.9% in those aged over 80 [5]. In Japan, the results estimated a 0.01% prevalence in the general population and 0.03% in those aged over 60 [6]. In another study on a Finnish cohort, the incidence was 1.58 for every 100.000 persons [7].

The comorbidities associated with NPH are: Alzheimer disease (15%), chronic high blood pressure (50%), hyperlipidemia (14%), and diabetes mellitus (20%) [6, 7]. The latter two factors increase the risk of developing NPH by doubling it, as compared to a normal patient [8]. Similarly, obesity and psychological stress, heart diseases, and strokes have also been named as contributory to the development of this pathology [8, 9].

Unfortunately, the criteria for NPH diagnosis remain uncertain. While some specialists consider it the most common form of hydrocephalus in adults, others contest its very existence [3, 10, 11].

NPH is difficult to diagnose due to its broad and general symptomology, commonly associated with old age. Thus, in individuals aged over 75, urinary incontinence is present in 20 to 30% of them, whereas 20% develop some kind of dementia and 20% show signs of ventriculomegaly [4]. Implicitly, the management of NPH is equally difficult, due to the complications associated with shunting. As such, the morbidity and mortality rates are 20% and 0.2%, respectively [12].

PHYSIOPATHOLOGY

The CSF is mainly secreted by the cells of the choroid plexus, other regions playing mainly a rather insignificant role. CSF's volume is between 125 and 150 ml, and its secretion varies between 400 and 600 ml daily, renewing itself 4 to 5 times every 24 hours in a healthy adult [13]. Its role is vital, namely, the protection and nutrition of the parenchyma [14]. Furthermore, its dynamic is highly dependent on the rate of production and absorption, as well as on the blood-related pulsatile flow through both the subarachnoid and Virchow-Robin spaces to the cerebral parenchyma [15, 16]. According to Adams et al. original theory, NPH develops when the level of CSF's reabsorption diminishes, thus resulting in intracranial hypertension, leading to ventricular dilation as a compensating mechanism [1]. Hence, a larger volume of CSF is redirected to the Virchow-Robin spaces, giving birth to a compression of the parenchyma and ischemia of the white matter.

The specific pathophysiology of iNPH is unclear, yet various mechanisms have been put forward as possibly involved in developing the pathology, such as [2]:

- Reduced compliance of the subarachnoid space
- Reduced reabsorption of CSF in the venous system
- Inadequate expression of TNF-alpha in CSF
- The hyperdynamic flux of CSF in the cerebral aqueduct
- The higher pressure of the CSF
- The reabsorption of CSF through abnormal mechanisms

CLINICAL PRESENTATION

iNPH must be suspected in older patients suffering from abnormal walking, sometimes combined with dementia or urinary incontinence [3].

Symptomatology can vary massively between patients. They may show signs with the classic triad in percentages of 30 to 50 (gait disturbance, urinary incontinence, and cognitive deficit), or only a combination of these: only gait impairment (5%), only dementia (2%), both combined (28%), gait abnormality together with urinary incontinence (4%) and dementia accompanied by urinary incontinence (1%) [6][17]. Approximately half of the patients with iNPH only show signs of a gait disorder, the other two characteristic symptoms being absent [6].

DIAGNOSIS

According to international guides, the imagistic diagnosis is based on the following elements [18]:

- Ventricular dilation with an Evans index > 0.3 [19]
- The absence of a macroscopic obstruction of the dynamics of the CSF
- At least one of the following [20]:
  - o Callosal angle exceeding 40° [21]
  - o Temporary dilated temporal horns of the lateral ventricles, but not fully due to the atrophy of the hippocampus
  - o Changes in the CT and MRI signal caused by the alteration of the content of cerebral water, not fully owed to the microvascular ischemic modifications or demyelination.
  - o Signs of a "flow void" in the MRI in the Sylvian aqueduct

The following imagistic methods can be engaged as well: MR elastography (MRE), glymphatic MRI, or the Silver index [22, 23, 24].

Regarding the Evans index, it is established based on a CT scan in the axial incidence. An index exceeding 0.3 indicates a pathological condition of the ventricles (sensibility of 80%) [19]. The threshold for indicating a pathological component

varies by age, namely: between 65 and 69 years – 0.34; between 70 and 74 years – 0.36; between 75 and 79 years – 0.37; between 80 and 84 years – 0.37 [19].

Callosal angles are measured based on a CT or MRI scan, at the median point of the corpus callosum [21]. Identifying this point necessitates using the sagittal plane, placed parallel to the floor of the fourth ventricle [21]. The limit was 105.4° (42% sensibility, 87% specificity) [21]. It is deemed that, with the decrease of every degree in callosal angles, a patient has a 4% greater chance of benefitting from a shunting surgery [21].

The Japanese guidelines for diagnosing NPH do not regard periventricular changes as relevant. However, they do include two new criteria of diagnosis, i.e. Sylvian fissures and enlarged basal cisterns, as well as the narrowing down of the subarachnoid space and the cerebral sulci at the median level of the brain [25]. In 2017, the efficiency of the two guides was debated, since there are significant discrepancies from the international medical practice, the former being substantially more specific, demanding the presence of at least two symptoms of the classic triad to confidently identify the diagnosis [26]. Furthermore, the study has underlined the necessity of a common system for diagnosis, more objective than the current one [26].

Clinically, several procedures could be executed to diagnose NPH. Firstly, "tap test" or CSF's evacuation test consists in removing 30-50 mL of CSF through a lumbar puncture, to improve the symptomology, the association of the gait function with the frontal assessment battery score, the improvement of verbal fluency and gait [25, 27, 28, 29]. Secondly, different weights can be given to the various markers from CSF, such as the expression of certain isoforms of transferrin, of the tyrosine phosphatase Q-type receptor, or has-miR-4274. Similarly, the correlation between slow vasogenic waves (SWV) and intracranial pressure must be investigated [30].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis must be performed with Alzheimer disease (AD), frontotemporal dementia, dementia with Lewy body, the one from Parkinson disease (PD), the one associated with AIDS, dementia caused through corticobasal degeneration and any other type.

Generally, the level of proteins in the CSF is measured, considered alongside biomarkers of the AD. In this particular case, the level of p-tau and t-tau are high, whereas the level of a β-amyloid peptide (Aβ) is low [4]. In the particular case of NPH, all these parameters are high, going back to normal values after shunting [31].

Apart from the AD, the PD, as well as other parkinsonian syndromes cause gait impairment [4]. Numerous investigations can be carried out, such as SPECT (Single Photon Emission Computed Tomography), this being limited through detecting an exhaustive set of neurodegenerative diseases, or FDG-PET (Fluorodeoxyglucose – Positron Emission Tomography), which can identify caudate hypometabolism, a potential marker of NPH [4].

TREATMENT

The clinical presentation of NPH is insufficient to recommend ventriculoperitoneal shunting surgery (VPS), because either one of the symptoms of NPH may have multiple potential etiologies. The diagnosis must be established clearly through the abovementioned methods in order to recommend surgical treatment.

VPS is the only efficient method of treatment for iNPH, by implanting a ventriculoperitoneal shunt. The international and Japanese guides, as well as AAN (American Academy of Neurology), confirm VPS as the only efficient method of treating iNPH, as opposed to the rather supposedly inefficient endoscopic approach of the third ventricle [25, 32, 33].

The purpose of a shunt is to drain CSF towards space where it may be reabsorbed. A shunt has three components: a proximal catheter, inserted at the level of the right lateral ventricle, a distal catheter in the peritoneal cavity, and a valve of shunting which contains a mechanism opening the valve up when the difference in pressure between the two cavities reaches a pre-established value [3]. Once the valve is open, CSF is drained in the peritoneum. Another approach is represented by lumboperitoneal shunt (LPS), which has the proximal end in the lumbar zone. In a study from Japan, it has been stated that LPS is used in 55% of the cases, whereas VPS is used in 43% of the surgical cases of NPH [6]. Another option of VPS is placing the distal end of the shunt between the two sheets of the greater omentum, the technique is considered as having good results and a low rate of post-surgery complications [34].

Concerning the efficiency of the shunting surgical treatment, in the first three months, in most cases, the headache is gone, and the gait deficit has improved in 85% of the cases, urinary incontinence in 70%, and cognitive functions in 65% [35].

In a study on the efficiency of LPS, it has been concluded that the method is comparable with VPS for patients showing signs of NPH. Nevertheless, the revision of the shunt took place more frequently in patients with LPS than in those with VPS [36].

Regarding the prognostic, 60% of the patients have benefitted from an improvement in symptomatology after the shunting surgery, and 40% have shown signs of significant improvement. These were measured using the mRS scale [9]. Both pre-surgery and post-surgery, patients must be evaluated using the following systems: Japanese NPH scale, Berg scale, DGI (Dynamic Gait Index), FIM (Functional Independence Measure), MMSE (Mini-Mental Status Examination), and TUG (Timed Up and Go) [2].

A series of post-surgery factors can suggest a good prognostic, such as: an aqueduct flux exceeding 42 µl, the absence of lesions of the white matter on MRI, resistance to the CSF debit exceeding 18 mmHg [2]. Antagonistic factors are severe dementia, dementia as a symptom of presentation and MRI abnormalities such as cerebral atrophy or lesions of the white matter [2].

Complications that may arise include:

• Surgical complications of the shunt: the failure of the shunt (3%), under- or over-drainage, subdural hematoma (3-4%), infections (1%) [37];

• Surgical complications unrelated to the shunt: seizures and intracerebral hemorrhage (under 5%) [2];

• Schizophrenia – 3 to 4 times more likely in patients with iNPH than in the healthy population [38];

• Hypertension and diabetes type 2 are frequent in iNPH patients, the latter risk factor causing increased mortality in affected patients [7].

CONCLUSIONS

NPH is a rare, yet treatable disease, and the diagnosis may be difficult to establish due to the rather broad symptoms. Both iNPH and sNPH cause similar features.

The difference between the idiopathic and secondary hydrocephalus has led to a difference in approach in a similar pathology, the latter being labeled as a surgical emergency. Both the concept of NPH, as well as the therapeutic approach retain a status of controversy. The diagnosis of iNPH must be considered when a patient shows signs either of the classic triad, or of some elements of it, or in the case of suggestive imagistic criteria.

Following this evaluation, treatment must be sought only when the risks and benefits of the shunt are carefully balanced. Recent innovations in the field of imaging have greatly improved the identification of patients who may benefit from shunting surgery. Furthermore, it should be also keep in mind that patients suffering from iNPH also present associated comorbidities, such as PD, AD, or other neurodegenerative diseases. Hence, the diagnosis must include tests that draw a clear distinction between NPH and these potentially present diseases. For the same reason, the patient's response to the drainage of CSF can be unpredictable.

NPH must be seen as a reversible cause of dementia. In the future, ample studies must be made to demonstrate the efficiency of shunting surgery.

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