

IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS (HAKIM-ADAMS SYNDROME): CLINICAL SYMPTOMS, DIAGNOSIS AND TREATMENT

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received: 3.7.2019;

revised: 20.9.2019;

accepted: 7.11.2019

SUMMARY

Idiopathic normal pressure hydrocephalus is a chronic steadily progressing disease. Nowadays a vital and acute socially significant problem still has not been solved. The etiology and pathogenesis of this disease remain so far poorly understood. Variable clinical manifestations, as well as difficulties in differential diagnosis with other neurodegenerative diseases - lead to underdiagnosing of the illness that causes a significant decrease in patient's quality of life and even results in disability. The number of patients with idiopathic normal pressure hydrocephalus has been steadily increasing. That is why, the coverage and a full study of this problem is of great interest for a broad circle of medical professionals.

Key words: hydrocephalus - ventriculoperitoneal shunt - cerebrospinal fluid - dementia - neurodegenerative diseases

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INTRODUCTION

Normal pressure hydrocephalus (NPH) is a characterized by an expansion of the ventricles of the brain against the background of normal intracranial pressure (ICP) values and manifested by a specific triad of symptoms including gait disturbance, cognitive disorders and dysuria (primarily urinary incontinence). For the first time NPH was described by the Colombian neurosurgeon Salomon Hakim Doe (1922–2011) in 1964, followed by a detailed and expanded analysis conducted by S. Hakim in collaboration with the American neurosurgeon Raymond Delesy Adams (1911–2008) in 1965 (Adams et al. 1965, Wallenstein & McKhann 2010). They paid special attention to the possible reversibility of clinical manifestations in this syndrome by adequate surgical treatment with ventriculoperitoneal shunting.

The prevalence of NPH is not understood completely. In various population-based epidemiological studies, the incidence of NPH is estimated to range from 0.3 to 3% among patients over 61 years of age (Jaraj et al. 2014). There is evidence of a significant increase in NPH incidence with age: Among those older than 80 years it was 5.9% (Rabiei et al. 2016). Analyzing the results of more than 7.5 million applications for medical care in Germany, the authors accounted the incidence of NPH 1.36: 100,000 per year (Lemcke et al. 2016). According to the majority of authors, the incidence of NPH in elderly population is about 0.5% (Trenkwalder et al. 1995, Hedera et al. 1998). Some Japanese researchers concluded that the occurrence of NPH among people over 65 years of age is 2.9% (Hiraoka et al.

2008). In Norway, health care workers and non-governmental organizations carried out extensive work aimed at identifying and selecting patients suffering from NPH during one year in a population of 220,000 inhabitants. They noted that the prevalence of NPH in the Norwegian population was over 21.9: 100 000 population; the incidence was 5.5: 100 000 population per year. However, the authors consider these rates underestimated (Brean & Eide 2008).

There are few reasons for a significant (up to 80%) underdiagnosis of this disorder. First, the main difficulty is the differential diagnosis of NPH and similar diseases, including neurodegenerative ones (Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Levy bodies, etc.) (Tisell et al. 2005, Kiefer & Eymann 2010). Secondly, the diagnosis of NPH is laborious; the daily work on the treatment of elderly patients with dementia is tedious. However, with gradual increase in the average age of the population, one can expect an augment in the number of elderly patients with NPH (Hebb & Cusimano 2001) including those in need of surgical treatment, which makes the treatment of such patients actual topic of studies. The shunting performed successfully, timely and according to the indications, can significantly improve the quality of life for patients with NPH and, as a result, relieve the burden for those taking care of them.

Due to the fact that the incidence of NPH increases with age, reaching a maximum between 70 and 79 years (Brean 2009), this age group should be under particular observation of medical professionals regarding its reveal.

ETIOLOGY AND PATHOGENESIS

The main theory that explains the development of NPH is the hydrodynamic concept proposed by D. Greitz in 2004 (Greitz 2004). According to it, the imbalance between secretion and reabsorption of CSF is a key link of NPH pathogenesis.

The importance of genetic predisposition for the development of NPH has been emphasized (Cusimano et al. 2011). Some tendency to NPH development among patient's close kinship was noted (McGirt et al. 2008). Recent review has summarized pathophysiology of idiopathic normal pressure hydrocephalus (iNPH) in details, emphasizing CSF pathways disorder, metabolo-neurodegenerative factors and heredity (Braütigam et al. 2019). Some authors relate NPH with the autoimmune disorders, like systemic connective tissue disorders, vasculitis and even chronic fatigue syndrome although probable linkage mechanisms are obscure (Higgins et al. 2017).

Depending on the detection of the immediate cause of the disease, NPH is divided into two subtypes: a) secondary NPH (sNPH) and b) primary or idiopathic NPH (iNPH), detected in approximately 40-60% of cases, more often in older patients when a history there is no indication of any clear cause underlying the development of the disease.

The most common reasons for sNPH include:

- Intracranial hemorrhage;
- Cranio-cerebral trauma (traumatic brain injury);
- Purulent-inflammatory processes in the cranial cavity;
- Surgical operations on the brain.

Up till now the etiology of iNPH has not been elucidated. Accordingly, any methods of etiotropic treatment for iNPH still do not exist. Existing methods of treatment (primarily, ventriculoperitoneal bypass) are palliative in nature and in many cases do not achieve complete regression of symptoms.

Attempts to determine the key links in the etiology and pathogenesis of NPH are closely related to the elucidation of the mechanisms of secretion, circulation and resorption of the CSF (Brinker et al. 2014), the characterization of structural changes in neurons and white matter of the brain, and changes in the composition of the CSF in NPH (Huovinen et al. 2016).

The progressive technologies detailed the structures of the brain participating in CSF "life cycle", which gave birth to the new views on the laws of its circulation, and role of its disturbances in many diseases, including NPH. The exchange of fluid between the intercellular, perivascular Virchow–Robin space and the subarachnoid space, as well as the exchange within the lymphatic system, has not been studied enough, and its changes in various pathological states can provide a key to the pathogenesis of a number of neurodegenerative

diseases and to the new methods of their differential diagnostics (Calcagni et al. 2013). An example is the increasing interest in studying the role of the lymphatic system in the clearance of cerebral beta-amyloid in Alzheimer's disease. It was found that this neurodegenerative disease is characterized by an imbalance between production and utilization of beta-amyloid. Such a metabolic shift significantly outpaces the manifestation of the disease. Previously, it was assumed that in the excretion of beta-amyloid, blood-brain and histohematic barriers play the main role.

In recent years the classical data about CSF exchange pathways were added by newly discovered brain lymphatic vessels (Louveau et al. 2015) and description of so called glymphatic system of brain, as well as communication between cerebrospinal and intracerebral interstitial fluid compartments with a possible key role of astrocyte aquaporins in brain glymphodynamics (Bacysinski et al. 2017). Lymph drainage from brain to cervical lymph nodes has been recently proven (Eide et al. 2018). Blood-brain barrier is no longer considered to be a "Chinese wall" isolating brain from immune interactions, but a field mediating neuroimmune communication (Tsygan et al. 2019).

New data indicate the presence of translational fluid flow through the aquaporin channels of the cells of the lymphatic system, which allows the utilization of a significant amount of beta-amyloid (Cherian et al. 2016).

Recently a number of researchers have been considering NPH as a potentially reversible neurodegenerative disease. It is likely that the positive effect brought in by liquor-shunting operations is also related to the improved excretion of beta-amyloid from brain via the ventricular system, which can render a beneficial effect on the functioning of the central nervous system (Bassar & Lippa 2016, Gavrilov et al. 2016).

There is a hypothesis by S.M. Iencean (2003), putting close two different disorders of CSF exchange, which both are prone to the same treatment with CSF drainage: Namely iNPH and idiopathic intracranial hypertension. In former ventricles are distended, but no CSF hypertension and high ICP occurs, in later – ICP is high, but with non-distended ventricles. The author believes, that glial-ependymal barrier between ventricles and brain interstitial space is "open" in idiopathic intracranial hypertension, but "closed" i.e. somehow preventing increase in intracerebral pressure – in iNPH (Iencean 2003).

Currently in Department of Neurosurgery of the S.M. Kirov Military Medical Academy we conduct a research of pathogenesis, diagnosis and treatment of iNPH, by electron microscopy of supravital brain biopsy samples and studies of CSF samples obtained during ventriculoperitoneal shunting from the patients with iNPH, in order to clarify the pathogenesis of Hakim–Adams syndrome and establish the methods for the differential diagnosis of similar neurodegenerative diseases.

CLINICAL MANIFESTATIONS

Nowadays iNPH is interpreted as a chronic, steadily progressing disease that significantly reduces the quality of life, especially in the absence of timely diagnosis and treatment, due to its disabling character (Hebb & Cusimano 2001). Most patients with NPH are over 65 years of age to the moment of diagnosis. Because of the variety of clinical manifestations and the difficulty of differential diagnosis with Alzheimer's disease and other diseases, patients with NPH often seek medical care not only from neurologists, neurosurgeons and psychiatrists, but also from representatives of most other medical specialties, for example, urologists and internists. Therefore, coverage and a full study of this problem are of interest to a wide range of medical professionals.

The NPH is characterized by a gradual development of the classical Hakim–Adams triad: Disorders of gait, dementia and urinary incontinence. However, it is essential that the classical picture, described in 1965, is observed only in half of the cases. In most patients, gait disturbance is the first symptom, then dementia occurs and later, pelvic disorders join. A fluctuation in the severity of symptoms is possible, although not typical in NPH.

One of the frequent complaints in patients suffering from NPH is dizziness, which they describe as a sense of instability in movement, e.g. in sharp bends of the trunk. In this case, dizziness is based on postural instability and dysbasia inherent in the disease. Disorders of locomotion in NPH include the elements of apraxia, a typical walking in the form of shuffling gait with short steps on widely spaced legs and loss of balance. In NPH, there are no changes in the movements of the hands during walking, which may distinguish it from Parkinson's disease. In the early stages, with minimal support, gait changes in patients with NPH may be insignificant.

As the disease progresses, the step height decreases, it becomes difficult for patients to tear their legs off the ground, there are difficulties in initiating the act of walking, turns are made in several stages and incidents often occur. In such cases, lying or sitting patients with NPH can mimic the movements of the legs, which they must but failed perform while walking. There is sometimes a correlation between the presence of arterial hypertension in NPH patients and the severity of NPH symptoms, especially as regards to walking disorders. Another diseases, which frequently happen in co-morbidity with NPH are diabetes mellitus and alcoholism (Braütigam et al. 2019, Iencean 2003). Muscle tonus in the legs, as a rule, is increased according plastic type or type of confrontation. In more severe cases of NPH occurs the following set of symptoms related to lower extremities: Spasticity, hyperreflexia, and pathological

stop signs. The presence of manifestations predominantly in the legs of NPH patients probably is explained with the fact that the motor pathways connecting the cerebral cortex with the lower extremities are located more medially – near the walls of the lateral ventricles, and the pathways to the upper extremities are located laterally, more distantly from the ventricles (Moretti 1985). The gait changes in NPH patients may also result from the dissociation of basal nuclei with the frontal cortex, dysfunction of the frontal cortex and violation of senso-motoric integration (Hattori et al. 2011).

Another important manifestation of NPH is dementia. Patients are characterized by the presence of cognitive disorder and disorientation (more in time rather in space). Often it is difficult for patients to set out the history of their case. In some rare cases, the hallucinations and mania were registered (Rojas-Estape et al. 2012). A characteristic symptom of NPH is also emotional lability. In general, cognitive impairments are manifested by a weak memory, a slowing of the rate of psychic and psychomotor reactions, a decrease in the ability to use acquired knowledge, as well as apathy, which is associated with dysfunction of the anterior parts of the brain and characteristic of so-called subcortical dementia (Damulin et al. 1999).

Cognitive impairment in NPH is not the dominant manifestation, especially for the début of the disease, when gnosis and other cortical functions are usually not altered. In contrast to Alzheimer's disease, memory impairments are not so obvious and mainly resulted from decrease in the functional integration of the frontal lobes (Toma et al. 2011). Severe dementia in patients with NPH implies either an unrecoverable pathomorphological defect (due to TBI, stroke, etc.), or in the presence of either concomitant Alzheimer's disease or vascular dementia. Neuropsychological scales sensitive to frontal disturbances (for example, Frontal Assessment Battery, FAB) are used to detect cognitive disorders in NPH, especially in the early stages of the disease. The frontal character of cognitive impairment in the case of iNPH may be due to the predominant extension of the anterior horn of the lateral ventricles, accompanied by a more significant dysfunction of the deep sections of the frontal lobes and anterior parts of the corpus callosum. It is believed that the basis of cognitive disorders accompanying NPH is the compression of the capillaries of the brain by increased hydrostatic tissue fluid pressure of the parenchyma, especially in view that positron emission tomography shows a diffuse decrease in glucose metabolism both in the cortex and in the subcortical areas (Jagust et al. 1985).

It is possible to identify complaints of patients for frequent urination and nocturia even in the early stages of the iNPH, by means of active, targeted questioning of a patient. As the disease progresses, imperative urges and periodic urinary incontinence are added. Patients

cease to feel the urge to urinate and are indifferent to the fact of involuntary urination, which is typical for the frontal type of pelvic disorders. Stools incontinence is rare, usually in patients at the late advanced stages of iNPH.

In addition to the triad of Hakim-Adams, neurological examination in NPH patients reveals postural tremor, a kind of akinetic-rigid syndrome characterized by the phenomenon of congealing, rigidity in axial muscles and limb muscles, also pseudobulbar syndrome and a grasping reflex can be noted.

Similar manifestations can occur with a wide range of diseases: Chronic occlusive hydrocephalus, Parkinson's disease, Alzheimer's disease, Binswanger's disease, vascular dementia, cerebral atrophy, spinal stenosis at various levels and a number of other illnesses. Despite the abundance of proposed diagnostic techniques: Radiation imaging methods – computed tomography (CT), magnetic resonance imaging (MRI) of the brain with calculations of the ratio of the volumes of the ventricles of the brain and its parenchyma, as well as the magnitude and degree of compression of subarachnoid spaces; identification of specific biochemical markers in the blood and liquor; invasive methods of diagnosis (tap test, extended external lumbar drainage and infusion-stress test) – so far none of mentioned above is able to reliably argue the need and predict the effectiveness of the liquor-shunting operation. This hardship can considerably complicate the differential diagnosis of NPH, and makes it urgent necessity to create a reliable algorithm for selecting patients for surgical treatment.

DIAGNOSIS

Timely and reliable diagnosis of NPH is relevant for solving the problems of evaluating the effectiveness of the treatment.

The complexity of diagnosis of NPH is associated primarily with the lack of a coherent concept of the etiology and pathogenesis of the disease, as well as the existence of diseases that have similar symptoms, such as Alzheimer's disease, various forms of parkinsonism, Binswanger's disease, vascular dementia, degenerative-dystrophic spine diseases, etc. For differential diagnostics of iNPH a number of radiological, laboratory and invasive methods was proposed, as well as plenty of methods for assessing cognitive and mnesic disorders. However, complete criteria for selection of patients for the implementation of liquor-shunting operations are not yet formulated. Still there are no reliable evidences on the advantages of these or those types of shunting systems, and the system of rehabilitation of patients who underwent surgical treatment has not been fully developed.

One of the main ways to diagnose iNPH is "tap-test" – a lumbar puncture with a single removal of a

sufficiently large amount of CSF (30-60 ml). In general, the initial liquor pressure in patients with iNPH usually does not exceed 200 mm of water and biochemical analysis of CSF usually does not reveal any abnormalities. Before and after the puncture, a quantitative analysis of cognitive functions is performed using neuropsychological tests, as well as gait evaluation with video registration.

The sensitivity of "tap-test" is low (about 60%); therefore, with negative "tap-test", prolonged external lumbar drainage ("long-term lumbar drainage test") is performed, providing long-term (up to 72 hours) and controlled outflow of liquor (10 ml/hour). The test results are also evaluated on the basis of an analysis of changes in cognitive disorders based on neuropsychological testing and gait analysis with video recording. It is possible to stop the test earlier than 72 hours after receiving a positive result.

Even a short-term clinical improvement allows considering the test positive and indicates the need for consultation by a neurosurgeon to resolve the issue of carrying out a liquor-shunting operation.

To evaluate the resistance to the outflow of liquor, an infusion-loading test is used, which consists in the endolyumbal administration of physiological solution for an hour at a constant rate (0.8-1.0 ml/min) under conditions of simultaneous recording of ICP or lumbar CSF against infusion. In the "lying on the side" position, the puncture of the terminal cistern is carried out on one level (L3-4) with two needles (18G). One of the needles is connected to a device that registers pressure, and the other is used for infusion of physiological solution. Normally, on the background of infusion, the liquor pressure reaches a certain constant value - the plateau - the level of pressure at which the resorption of the CSF is in equilibrium with the liquor production and infusion of the solution. The resistance level of the outflow of CSF more than 18 mm Hg/ml/min is considered pathological (positive test result).

One of the modern methods for NPH diagnosis is monitoring ICP. The method consists in implantation of a lumbar or ventricular catheter and registration of ICP for 24-72 hours. Patients with NPH have pathologically high values of ICP, especially in the phase of fast sleep, which is associated with vasodilatation and increased blood flow in the brain during this period. Variations in ICP are associated with the existing functional obstruction of CSF outflow from the ventricular system to the subarachnoid spaces due to the difficulty of reabsorption of the CSF and a decrease in the gradient between CSF pressure in the ventricles and on the convective surface of the brain. To increase the accuracy of the method, ICP monitoring should be carried out in synchronism with polysomnography. This method is not used in routine diagnostic practice due to high risk of trauma.

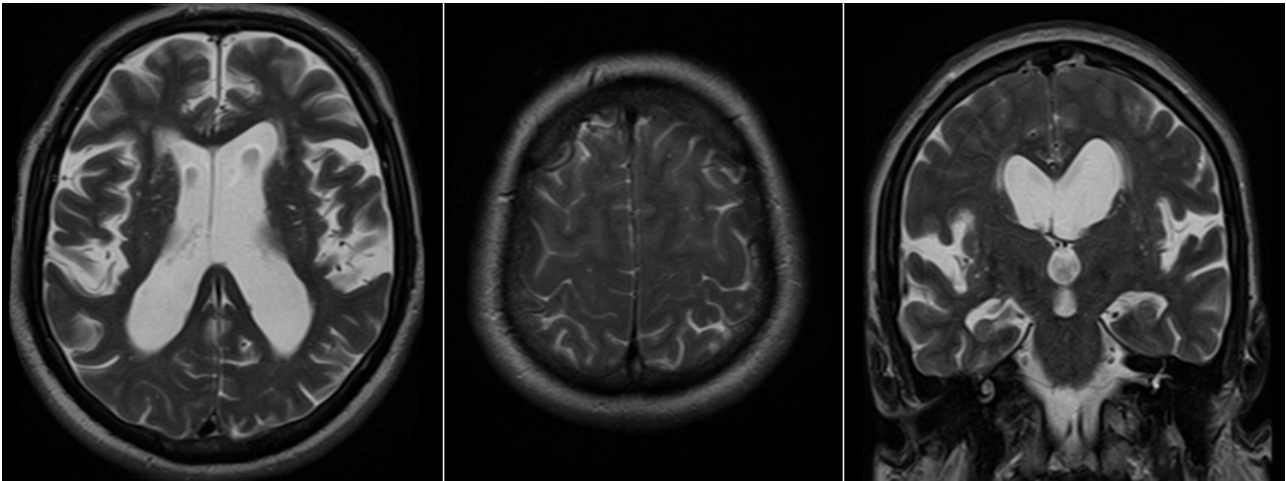


Figure 1. MRI of the brain of the patient with iNPH. The enlarged ventricles of the brain and lateral cracks are visualized, while the subarachnoid spaces of the convective surface and the interhemispheric cleft are narrowed (DESH-syndrome). The case observed by authors

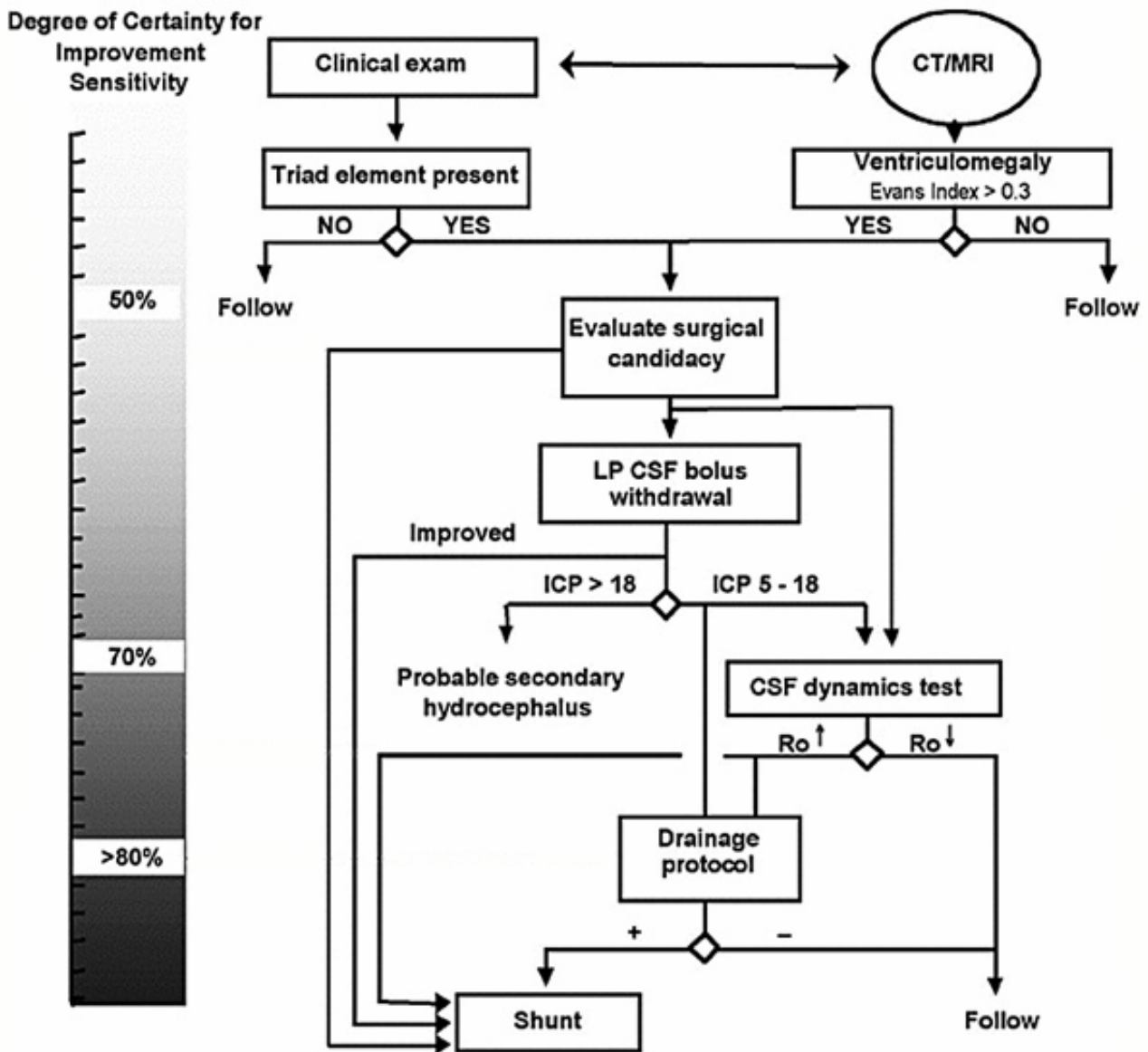


Figure 2. Scheme of selection of candidates (with probable iNPH) for surgical intervention (Marmarou et al. 2005, Tsygan et al. 2019)

It is important to note that in patients with ophthalmoscopy, there are no stagnant changes in the fundus. According to electroencephalography data, non-specific changes in brain bioelectrical activity, characterized by the predominance of low-frequency (slowly wave) characteristics, are revealed in NPH.

The results of neuroimaging methods of investigation (CT and MRI), which allow to detect ventriculomegaly, are of leading importance for the diagnosis of iNPH. In most cases, along with ventriculomegaly, there is a disproportional expansion of subarachnoid spaces. In particular, the lateral crevices are sharply widened, and the cortical grooves of the convectional surface and the interhemispheric fissure remain within the norm or are slightly widened (Figure 1), which is better estimated on the coronary section of the MRI. In 2010, the Japanese Committee for the Treatment of NPH, this MR-picture of hydrocephalus was named "DESH", an abbreviation of English "Disproportionately Enlarged Subarachnoid-space Hydrocephalus" (Jagust et al. 1985).

Also, exclusion of other reasons for hydrocephalus is possible by means of brain MRI. Detection of small ischemic foci or areas of leukoarosis does not rule out the diagnosis of iNPH, since it is possible to have iNPH and cerebrovascular insufficiency combined. As it is shown above (Figure 1), the temporal and anterior horns of the lateral ventricles are particularly significantly enlarged, which leads to the appearance "butterfly"-shaped figure on the axial sections. The widening of the anterior horn of the lateral ventricles with iNPH reaches 30% or more of the transverse dimension of the skull at the level of the cut (Hashimoto et al. 2010, Marmarou et al. 2005).

Diagnostic criteria of iNPH for the purpose of selection of candidates for surgical intervention, in accordance with the world recommendations, are given in the scheme (Figure 2) (Marmarou et al. 2005).

TREATMENT

Treatment of patients with NPH, having a positive test result, should be operative one. The indications for the surgery are determined on the basis of the sum of the clinical symptomatology data (complete or incomplete triad of Hakim-Adams), the hydrocephalus picture according to the MRI (CT) and the results of the tests (positive test results are an absolute indication for surgical treatment). There are no methods of effective conservative treatment for patients with NPH. As a temporary measure to reduce the CSF production, patients with NPH can be treated with Diacarb® (Acetazolamide) (Golden & Bonneman 1998).

The basis of treatment is liquor-shunting surgery with the implantation of ventriculo-peritoneal or lumbo-peritoneal shunts, in which a positive effect is

achieved in 60-80% of patients. In the far-advanced stages of the disease, when there are already irreversible changes in the brain, the prognosis of surgical treatment worsens. Complications after shunting (excessive drainage, subdural hematomas, insufficient drainage, and dysfunction of the shunt) are noted in 20-30% of patients. For the prevention of complications, an individual shunt selection is recommended. Currently, in connection with the appearance of externally adjustable (programmable) valve systems with antisiphon device, as well as catheters impregnated with antibiotics or silver, the number of complications has significantly decreased and in specialized institutions is no more than 5-10%.

The restoration of the ability to move independently, the normalization of cognitive functions (short-term memory and orientation in space, time and self) and the elimination of urinary incontinence can significantly improve the quality of life, even despite the short-term effect (usually 3 to 5 years). Shunting in patients with NPH is aimed at improving the quality of life. This operation can be included in the sphere of functional neurosurgery, as well as, for example, the surgically-mediated stimulation of deep brain structures in Parkinson's disease. Although any surgical intervention is risky, shunting with modern shunting systems has an acceptable frequency of complications. This circumstance makes the intervention preferable for cases with the established diagnosis.

In the postoperative period, patients with NPH should undergo a comprehensive rehabilitation and recovery treatment under the supervision of a neurologist and rehabilitation specialists. It is necessary to monitor changes in the neuropsychological state, gait and pattern of MRI. With recurrence of symptoms, a neurologist and neurosurgeon are called in for examination, sometimes further reduction in the opening pressure of the valve of the shunting system is necessary or, in case of dysfunction of the shunt, the replacement of the valve or the entire system is required.

CONCLUSION

Nowadays iNPH is regarded as a socially significant and still unsolved problem of current interest in biomedicine and in health care. In its current imagination, iNPH is a chronic, steadily progressing disease that significantly reduces the quality of life of patients, in the absence of apt diagnosis and treatment, acquires a disabling nature. Unfortunately, until now many patients with iNPH while being outside the observation of medical doctors, remain under-surveyed. Such patients may also stay under observation of neurologists, but due to other about "competitive" diseases.

Because of broad spectrum of clinical manifestations and the difficulty of distinguishing from Alzheimer's disease and few other diseases, patients with NPH seek for medical care not only from neurologists, neurosurgeons and psychiatrists, but also from representatives of most other medical specialties, for example, urologists and internists. Therefore, broad coverage and a full study of this problem are of interest to a wide range of medical professionals. After all, the liquor-shunting operation if performed successfully and according to the indications, can significantly improve the quality of life for patients with iNPH and, finally, the quality of life for their relatives and friends taking care of these patients. For successful treatment of NPH the team, where besides neurosurgeon few other specialists should be included (neurologist, psychiatrist, rehabilitation specialist, urologist) – needs considerable experience working together and, most importantly, conducting a clinical and pathophysiological analysis of the results of the examination and treatment in order to improve the quality of care.

Acknowledgements:

The work is supported by the grant from Russian Federation Government, contract # 14.W03.31.0009.

Conflict of interest : None to declare.

Contribution of individual authors:

Gaspar V. Gavrilov, Boris V. Gaydar & Leonid P. Churilov had substantial contribution to the conception and design of the study.

Gaspar V. Gavrilov, Alexander E. Korovin, Igor N. Samarcev & Dmitry V. Tovpeko had substantial contribution to the literature searches and analyses.

Dmitry V. Svistov, Alexander E. Korovin & Leonid P. Churilov drafted the manuscript and revised it critically for important intellectual content, and approved the final version.

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