ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ, ΒΙΟΔΕΙΚΤΕΣ ΚΑΙ ΑΚΤΙΝΟΛΟΓΙΚΑ ΕΥΡΗΜΑΤΑ ΣΤΟΝ ΙΔΙΟΠΑΘΗ ΥΔΡΟΚΕΦΑΛΟ ΦΥΣΙΟΛΟΓΙΚΗΣ ΠΙΕΣΗΣ

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Περίληψη

Ο ιδιοπαθής υδροκέφαλος φυσιολογικής πίεσης (iNPH) είναι μια νοσολογική οντότητα που εμφανίζεται συχνά σε ηλικιωμένο πληθυσμό προκαλώντας διαταραχή στη βάδιση ή/και στην ισορροπία, γνωστική έκπτωση και ακράτεια ούρων. Ο επιπολασμός του iNPH είναι περίπου 3,7%. Υπάρχουν πολλοί ασθενείς οι οποίοι δεν λαμβάνουν ποτέ βαλβίδα. Αυτό οφείλεται στο γεγονός ότι η νόσος έχει ύπουλη έναρξη και εξελίσσεται σταδιακά, ενώ η πλειοψηφία των ασθενών δικαιολογούν τα συμπτώματα τους με την αύξηση της ηλικίας τους. Η διαφορά σε σχέση με νευροεκφυλιστικές παθήσεις είναι ότι αντιμετωπίζεται με χειρουργική επέμβαση παροχέτευσης βελτιώνοντας τα συμπτώματα μέχρι και 84%, και γι' αυτό κατατάσσεται στις δυνητικά «αναστρέψιμες άνοιες». Ως εκ τούτου, ο iNPH είναι μια μεγάλη πρόκληση για τους νευρολόγους λόγω των δυσκολιών στη διάγνωση ασθενών που είναι κατάλληλοι για χειρουργική επέμβαση και πρόσφατα δημοσιευμένες μελέτες επικεντρώθηκαν στον εντοπισμό αυτών των ασθενών. Η φυσική πορεία του iNPH είναι μια σταδιακή επιδείνωση της συμπτωματολογίας με επιδείνωση της βάδισης και έκπτωση της νοητικής λειτουργίας με συνοδό διαταραχή της ούρησης. Η άλλη πρόκληση είναι να κατανοήσουμε τον παθοφυσιολογικό μηχανισμό πίσω από αυτήν την ασθένεια. Οι κατευθυντήριες γραμμές του iNPH αλλάζουν και υπάρχει συνεχής προσπάθεια διαφοροποίησης των ασθενών με iNPH από νευροεκφυλιστικές παθήσεις. Η έλλειψη σαφών κριτηρίων για τη διάγνωση του iNPH καθιστά την αναγνώριση των ασθενών με iNPH δύσκολη. Ασθενείς με iNPH χωρίς θεραπεία μπορούν εν μέρει να επιτύχουν τα ίδια μετεγχειρητικά αποτελέσματα που θα είχαν, αν είχαν υποβληθεί σε χειρουργική επέμβαση με βαλβίδα παροχέτευσης έγκαιρα. Στόχος αυτού του άρθρου είναι να ανασκοπήσει σύντομα τη βιβλιογραφία και να αναζητήσει έναν πρακτικό τρόπο σκέψης.

Λέξεις ευρετηρίου: υδροκεφαλία, παθοφυσιολογία, βιοδείκτες, Radscale, CSF tap test

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PATHOPHYSIOLOGY, BIOMARKERS AND RADIOLOGICAL FEATURES IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUSS

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Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is a disease that often appears in elderly population causing gait and/or balance disturbance, cognitive decline and urinary incontinence. The prevalence of iNPH is around 3.7% and there are a lot of unidentified patients who never receive a shunt. The disease has an insidious onset and progress gradually and the majority of patients use as a possible cause age related reasons. The difference with neurodegenerative diseases is that it is treatable with a shunt surgery and this

can improve patients' symptoms as much as 84% raising the hypothesis of reversibility. Hence, iNPH is a big challenge for the neurologists because of the difficulties to diagnose patients suitable to shunt surgery and recently published studies focused to identify this control group. The other challenge is to understand the pathophysiological mechanism behind this disease. The guidelines of iNPH are changing and there is a continuous effort to differentiate iNPH patients from other neurodegenerative diseases. The lack of golden standard for diagnosis of iNPH makes the identification of iNPH patients challenging. The natural course of iNPH is a deterioration of symptomatology with worsening of gait, balance urinary disturbance and cognitive decline and patients with untreated condition can partially achieve the same results they would have experienced if they had undergone shunt surgery in good time. Therefore, the aim of this article is to shortly review the literature and come to a practical way of thinking.

Key words: hydrocephalus, pathophysiology, biomarkers, Radscale, CSF tap test

INTRODUCTION

Short History

The recognition and discovery that there was "water" in the center of the brain impressed the doctors from the beginning of medicine history since thousands of years. Doctors tried to find the cause and explanation of the existence of water in the brain center. In ancient Greece the characteristic malformation caused by the increase of "water" in oversized head and the "Olympius" face classified the disease as one of the "holy diseases" and was the reason that the philosophy was involved in medicine. It was believed that from the ventricular system, in the center of the brain, the water was the filter for the refinement of the human soul. The first observations and descriptions of the occurrence of "brain water", as well as the first therapeutic interventions to cope with excessive growth, are attributed to the ancient Greeks. Hippocrates (460-370 BC) is known as the first physician who described and tried to treat hydrocephalus (hydro = water, cephalus = skull). Hippocrates was the first to suggest catheterizations of the ventricular system [1]. Herophilos from Alexandreia (325-255 BC), often called the anatomy's father, wrote about the ventricular system and about the fourth ventricle, the meninges, and tried to explain their function [2]. Galinos (128-200 BC) and Orivasios (325-405 BC) introduced thoughts about hydrocephalus [3]. Salomón Hakim described in 1964 normal pressure hydrocephalus (NPH) as a syndrome with normal cerebrospinal fluid pressure causing gait apraxia, cognitive impairment, and urinary incontinence, responding to shunt [4].

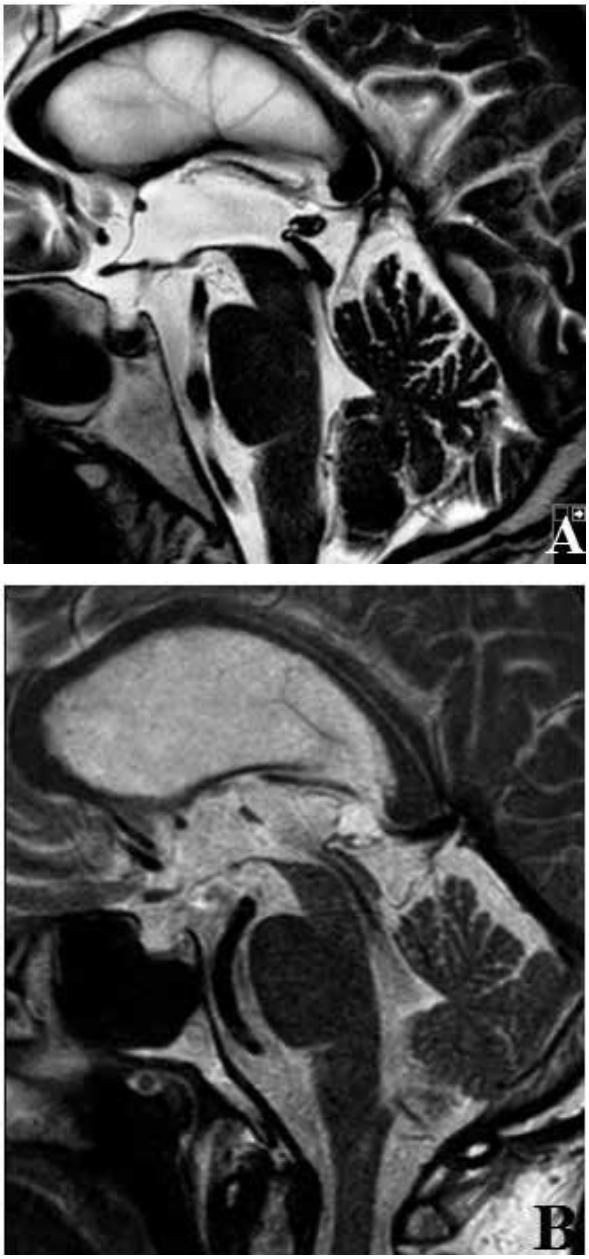
Clinical approach

The most common symptoms in hydrocephalus are a symmetrical broad based, short-stepped gait, unexplained impairment of balance, frontal-subcortical pattern of cognitive impairment and urinary urgency or urinary incontinence [5-7]. Gait test compatible to hydrocephalus disease appears with decreased step-height and length, decreased cadence, magnetic gait, increased trunk sway during walking, turned-out toes on walking, widened standing base, turning bloc and retropulsion. Cognitive impairment and dementia is another common symptom with involvement of the prefrontal brain areas causing executive dysfunction, slow psychomotor function with relatively intact recognition memory but with poor retrieval memory. Urinary urgency or incontinence is also common symptoms in iNPH but they are poorly described in the literature. A recently published study described bowel impairment in patients with hydrocephalus compared to healthy individuals [8]. A small study with hydrocephalus patients reported significant reduction of ganglion cell layer, suggesting an ongoing neurodegenerative process due to altered cerebrospinal fluid (CSF) dynamics [9]. Other symptoms such as depression, apathy, agnosia, seizures have been described in case control studies as uncommon symptoms of iNPH [10-12] [13, 14]. The prevalence of iNPH according to a Swedish study was estimated at 0.2% in individuals with an age of 70-79 and rising to 5.9% for individuals with an age higher than 80 years [15]. So far, there seems to be no difference in gender distribution [16].

The Computer Tomography (CT) or the Magnetic Resonance Imaging (MRI) of the brain shows expanded ventricular system, where other diseases cannot explain the patient's symptoms.

Hydrocephalus (HC) is divided into communicating and non-communicating HC (figure 1a and figure 1b). Communicating HC can be further divided, to secondary normal pressure hydrocephalus (sNPH), where the underlying cause is known, for example, following a subarachnoid hemorrhage and meningitis, and idiopathic NPH (iNPH) where no underlying cause can be found (figures 2 and 3). Furthermore, in last years, there is increasing number of reports on familial iNPH which indicates a potential genetic component and leads to a wide recognition of a third form of NPH, familial NPH (fNPH). Unlike sNPH, iNPH is difficult to distinguish from other neurologi-

Figure 1. A: non communicating hydrocephalus; B: communicating hydrocephalus



cal states with the symptoms of motor, cognitive and urinary incontinence in the elderly. Patients with iNPH are classified as "probable", "possible" and "unlike" [16].

Shunt is the only current treatment in iNPH established since 1951 by Nulsen, Spitz and Holter [17]. The aim of the treatment is to reduce the amount of CSF in the ventricle system and thus normalize the volume in the ventricular system. The standard treatment is surgery with a shunt placed from the ventricular system in the brain to the cardiac atrium, to the chest cavity, bladder, and most placed in the abdomen in peritoneal space. There is no consensus regarding the indications for surgery, but there are

Figure 2. On the left up side the normal ventricular system, on the right bottom secondary hydrocephalus caused by bilateral posterior infarcts

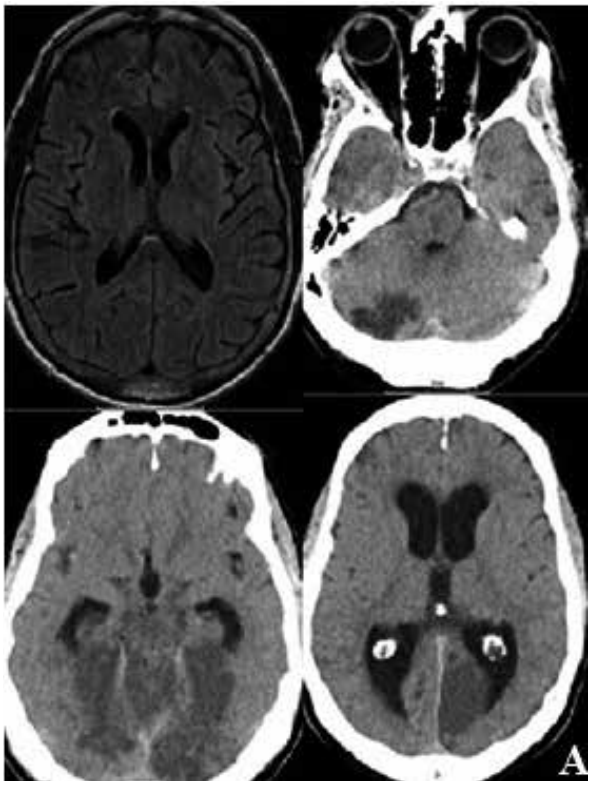
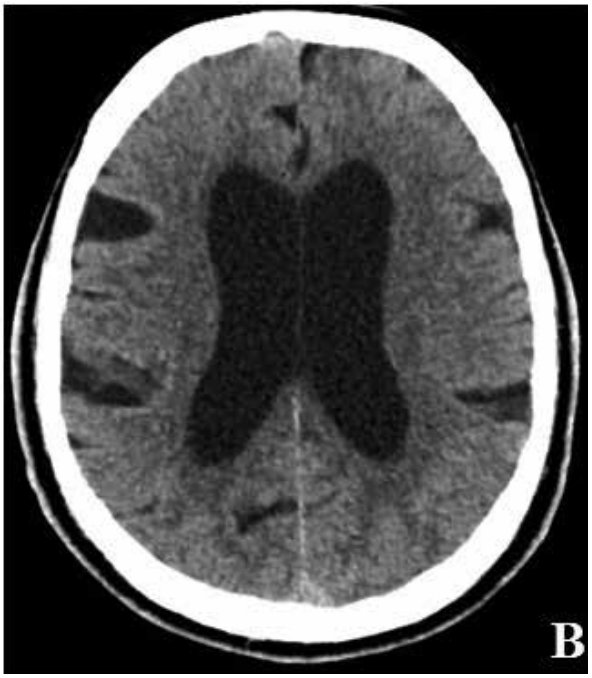


Figure 3. Typical picture of idiopathic normal pressure hydrocephalus



guidelines, both International-European and Japanese [18-21]. Usually, those patients exhibit the abovementioned symptoms in combination with typical ra-

diological imaging are considered for surgery. Almost 80% of iNPH patients improve their motor function but there are still a 20% of patients without any difference before and after a shunt operation [22].

However, the symptoms seen in NPH are common in elderly and may have many other causes. It can also be difficult to distinguish the radiological image from that seen in brain atrophy. Patients with Alzheimer's disease (AD) or subcortical vascular disease may appear to have large ventricles on the Computer Tomography or MRI image because of cerebral atrophy. They may also have similar symptoms to normal pressure hydrocephalus that are related to different degrees of white matter ischemia [16].

PATHOPHYSIOLOGY

In 50% of patients with NPH, no known cause can be identified. The underlying pathophysiology of iNPH remains unknown. The CSF space is a dynamic system, which constantly adapts its pressure to keep it stable. It responds to changes in CSF formation or reabsorption rates, arterial and venous flow, compliance of the intracranial structures and fluctuations in intracranial pressure (ICP). This process is important to ensure the correct functioning of the brain. Indeed, the brain is enclosed in a fixed structure and any volume increase needs to be matched by a decrease to avoid changes of the intracranial pressure and consequential functional abnormalities. The volume of blood entering the brain varies with the cardiac cycle, being present a net intracranial inflow of blood during systole and a net outflow during diastole. Arterial supply to the brain is pulsatile, while venous flow does not. This mismatch generates transient rises in CSF pressure. The system compensates for this in two different ways. First, the blood vessels can smooth the arterial blood influx modulating their compliance. Second the CSF flows through the cerebral aqueduct in response to pulsatile blood flow, thus maintaining intracranial pressure stable. When these processes are altered, compensatory strategies are applied. However, the compensatory mechanisms that keep the CSF pressure constant may also produce other pathological alteration. In iNPH, the compliance of the system is reduced, especially in the vessel of the superior sagittal sinus. This lack of arterial compliance is initially countered by increases pulsatile CSF flow through the aqueduct, but as the amplitude of arterial pulsatility increases, the blood flow in systole induces large ICP pulsations, determining the "water hammer" effect. These exaggerated pulsations cause venous damage in the periventricular region and displace the brain toward the skull, thus determining the development of hydrocephalus [23-25].

A lot of other hypotheses suggest structural or tissue distortion, reserve of CSF and interstitial fluid flow, failure of drainage of vasoactive metabolites, watershed ischemia in the deep white matter, impairment of periventricular cerebral blood flow autoregulation and dysfunction of CSF circulation or hydrodynamics. Abnormalities of CSF secretion, circulation and absorption can lead to excessive accumulation of CSF in the ventricular system and the development of hydrocephalus. Disturbances of CSF absorption play an important role in the development of hydrocephalus. It is of interest that review of the literature reveals a very high incidence of hypertensive and/or arteriosclerotic cerebrovascular disease in patients with idiopathic normal pressure hydrocephalus. The few published autopsy and biopsy studies of iNPH or NPH patients have not revealed any specific neuropathological pattern for NPH.

Cerebrovascular and neurodegenerative, including Alzheimer's changes, are present in many NPH patients. Leptomeningeal fibrosis has been found but does not correlate to CSF outflow [26-28]. In the iNPH-CrasH study presented that hyperlipidemia, diabetes mellitus, hypertension, mental inactivity, cerebrovascular disorders such as peripheral vascular diseases, obesity and psychosocial factors were over-represented in iNPH patients [29]. Tullberg et al in two previous studies found increased neurophilament (NFL) and glial fibrillary acidic protein (GFAP) in NPH patients but no correlation of interest was found between GFAP and NFL and NPH symptoms [30],[31]. In a third study of the same institute the preoperative NFL levels in NPH group correlated with overall improvement in gait and balance [32]. In a fourth study including NPH patients found elevated NFL levels preoperatively and a trend level with lower levels of NFL in patients with longer disease duration. Higher NFL levels correlated significantly with worse gait, psychometric and overall performance [33]. Tullberg et al in a study with 18 iNPH patients higher NFL was correlated with significantly poorer preoperative performance [34]. Tarkowski et al found high preoperative NFL levels in NPH patients [35]. Leinonen et al in a study with 35 suspected iNPH patients looked at the CSF biomarkers in positive and negative external lumbar drainage patients and found that NFL was pathologically increased similarly in both groups. Mean β-amyloid did not differ significantly between the groups. T-tau increased significantly with the age [36]. Jeppsson et al in a study with iNPH patients found elevated NFL and lower tau levels in patients with iNPH than in healthy individuals. Postoperatively, NFL increased, and t-tau decreased [37]. Pyykkö et al in a study with 53 iNPH patients found that iNPH patients with positive shunt response had a tendency towards lower NFL levels in ventricular CSF compared to shunt non-responders iNPH patients. Their interpretation of their result was that as NFL reflects subcortical axonal damage. Perhaps high NFL

could represent more severe and less recovery injury in the hydrocephalic brain [38]. Jeppsson et al in a study with 20 iNPH patients and 20 neurologically healthy controls found no difference of significance in NFL [39]. Abu-Rumeileh et al in a study with 71 iNPH and 50 healthy individuals showed significantly lower levels of aβ42, aβ40, t-tau, p-tau compared to healthy individuals. NFL levels were increased in iNPH [40]. Jeppsson et al in a study with 82 iNPH patients and other neurodegenerative conditions reported lower p-tau concentration in the iNPH groups compared with non-iNPH group and healthy individuals [41]. Manniche et al in a study with 28 iNPH patients, 30 subcortical ischemic vascular disease, 57 AD and 33 healthy controllers found lower NFL, aβ42 and t-tau levels in iNPH patients. NFL and aβ42 were the most reliable biomarkers to differentiate iNPH from subcortical ischemic vascular disease [42].

Currently, the genetic and molecular pathogenesis of iNPH is undetermined. One study showed a large family with three-generation NPH patients, who had clinical and MRI findings that cannot differ from iNPH . In a study by Korhonen et al. the prevalence of the C9ORF72 expansion in Finnish iNPH patients reported higher than expected giving the suspicion of connection between frontotemporal dementia and iNPH. Eleftheriou et al described identical twins with iNPH but not further genetic analysis was performed [14, 43-45].

The most common neuropathologies in patients with iNPH are vascular and Alzheimer's disease (AD)-related changes [46]. Amyloid plaque has been reported in brain biopsies from patients with iNPH and proposed as a significant feature of the pathology. In iNPH patients the rate of amyloid deposition is higher than in cognitively normal elderly subjects, but no differences in the probability of the apoE4 carriers observed [47]. Presence of apolipoprotein E4 (APOE4) allele is associated with increased risk of AD. The APOE distribution did not differ significantly between the iNPH patients and control population [48].

Besides small vascular disease Alzheimer's disease (AD) coexists frequently [49]. Frontotemporal dementia (FTD) has been also listed as a comorbidity in iNPH [44, 50].

CSF REMOVAL – CSF TAP TEST

The CSF tap test (CSF TT) is an invasive test that helps to diagnose possible disturbance in cerebrospinal fluid dynamics. The test starts with the patient in recumbent position. The doctor performs a lumbar puncture and once CSF is obtained, a spinal manometer connects to measure the CSF pressure in cm H20. For iNPH diagnosis the CSF opening pressure is expected to be 5-18 mm Hg (70-245 mmH20).The pressure is measured during a period of about one minute to avoid any artificially elevated levels, the patients have to be relaxed and their neck has a neutral position, the legs are extended. For the CSF TT 35-50 ml CSF is removed and the patients symptoms (especially gait and balance) are assessed before and after the CSF TT [51]. According to a review of eight CSF studies 73-100% experienced a good positive predictive value [52]. The negative predictive value of CSF TT was 18%-50%, meaning that patients with a positive CSF TT have a good prognosis to respond to a shunt surgery but a negative result from a CSF TT cannot rule out patients from surgery [53]. Extended 3 days CSF TT with the use of lumbar drainage have been used in previous studies but even with this test, a negative result could not rule out the possibility of response of a shunt surgery showing a positive predictive value of 80%-100% and a negative predictive value of 36%-100% [54] [55] [56]. Recently published study showed clear limitations of the CSF TT for selection of shunt eligible patients [57].

RADIOLOGICAL FEATURES

The presence of ventriculomegaly itself is not sufficient to diagnose iNPH. It is a common finding in elderly people due to the brain atrophy and is even more often seen in patients with AD. The perihippocampal fissure is dilated in AD, but not in iNPH.

Malm et al. and Momjian et al. considered that there may be a subcortical ischemia caused by CSF in combination with cerebrovascular disease [25, 58]. Flow MRI studies in patients with iNPH showed that the arterial pulse volume is reduced by 35%, and that the aqueduct stroke volume is elevated compared to normal, but similar results were also found in patients with dementia [23]. By introducing a shunt, the dysfunctional CSF system normalizes.

The combination of radiological findings and clinical features supports the identification of iNPH patients. However, the diagnosis of iNPH is challenging due to other neurodegenerative diseases with similar clinical symptoms and radiological picture [25]. Clinical experience presents that not all the ventriculomegaly patients, who meet all the criteria for iNPH, improve after a surgical intervention [24]. Alzheimer's disease (AD), vascular Dementia (vD), Parkinson's Disease, periventricular microangiopaty and other white matter diseases represent this group. The pathophysiology of white matter involvement is still poorly understood.

To understand how symptoms are improved in relation to the pathophysiology of iNPH, it is necessary to use techniques that can explore all lesions in the functional and anatomical structures involved in the disease. CSF withdrawal tests, intracranial pressure recording, or resistance measurement has been evaluated. Minor invasive techniques have also been

investigated, including CSF flow measurement with MR-velocity-sensitive pulse sequences or proton magnetic resonance spectroscopy (H-MRS) and in recent years also diffusion tensor imaging (DTI).

The periventricular tissue is characterized by disruption of the ependyma, oedema, neuronal degeneration, and gliosis, probably because of the altered dynamics in the extracellular fluid. These periventricular changes are referred to as smooth periventricular hyperintensity at the MRI. Microangiopathy changes near the ventricle system can present in both iNPH patients and vascular patients such as Binswanger Disease patients. Because of that, in the last years there is an increasing interest in white matter changes in iNPH patients. Using DTI is the most recognized method to examine white matter pathology [59]. The diffusion tensor was originally proposed for use in MRI by Peter Basser in 1994 [60, 61]. The introduction of the diffusion tensor model allowed, for the first time, a rotationally invariant description of the shape of water diffusion. The combination of 2D diffusion-weighted images, including diagonal elements, to a 3D diffusion assessment creates a high-resolution MR technique, which can reveal integrity periventricular white matter changes [62]. DTI describes the diffusion of water molecules using a Gaussian model. Technically, it is proportional to the covariance matrix of a three-dimensional Gaussian distribution that models the displacements of the molecules. By using this technique, we achieve to measure three eigenvectors and three eigenvalues. The three positive eigenvalues of the tensor (ε1, ε2, ε3) give the diffusivity in the direction of each eigenvector [63]. DTI integrity changes are quantified by apparent diffusion coefficient (ADC), which shows the diffusion changes and fractional anisotropy (FA), which presenting ADCs directivity [64]. Increased FA indicates compression of white matter and decreased FA is pointed out with axonal degeneration or brain oedema or both [65] [66, 67]. DTI is a non-invasive diagnostic promising tool which has been used in patients with iNPH. DTI has an huge ability to explore and visualize white matter and has been used as a possible diagnostic utility in patients with multiple sclerosis for quantification of brain white and grey matter damage in different MS phenotypes [68, 69], epilepsy for visualization of cyto-architecture distortion by appealing increased diffusivity and decreased AF [70].Trying to approach a possible explanation of iNPH's onset and to differential diagnose from other entities in early disease stage is challenging. DTI has been used in several research groups.

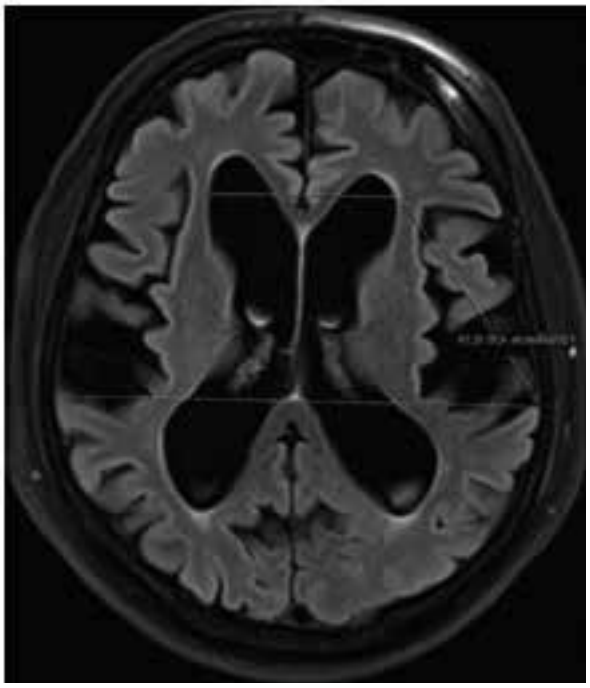
Radiological studies with the use of cerebral blood flow (CBF) revealed a reduced perfusion in the periventricular white matter compared to the perfusion of the subcortical white matter in iNPH patients [58, 71-73]. In studies focused on neuropathological findings, micro infarctions, lacunar infarction, microangiopathy and axonal loss to the frontal area has been described [26]. Other studies referred to the existence of AD-related CSF biomarkers in patients with iNPH and observed non-neuroinflammation in both diseases [27, 28, 38, 74].

During the last years, there is a continuous effort for more specific quantification of brain microstructure, by using diffusion MRI, and develop white matter models consisting of several compartments such as orientation, volume, fraction and diffusivity [75]. For example, the Composite Hindered and Restricted Water Diffusion (CHARMED) model provided sensible maps of axon density in vivo [76]. Measurements and simulations of diffusion in white matter using CHARMED provided an unbiased estimate of fiber orientation with consistently smaller angular uncertainty than when calculated using a DTI model or with a dual tensor model for any given signal-to-noise level. Furthermore, another paper introduced neurite orientation dispersion and density imaging (NODDI), a practical diffusion MRI technique for estimating the microstructural complexity of dendrites and axons in vivo on clinical MRI scanners [77]. Such indices of neurites can be used to map over the whole brain and presents new opportunities for understanding brain development and disorders.

Smith et al. introduced 2006 a new technology called Tract-Based Spatial Statistics (TBSS) [71]. TBSS aims to improve the sensitivity, objectivity, and interpretation of multidisciplinary diffusion formation studies. The purpose of TBSS was also to examine the whole brain and not just specific sites with single manual coated ROIs. This was like a calculated group mean FA-skeleton which improves a general model that can be automatically performed on all individuals who investigated by DTI. Liu et.al and Kern et al. performed TBSS in patients with MS, Knake et a. in PSP patients, Domin et al. in juvenile myoclonic epilepsy, Alves et al. in Alzheimer's patients, Liu et al. in temporal lobe epilepsy patients and in chronic schizophrenia patients. The method is not widely introduced in iNPH patients, but gives the opportunity to understand white matter changes in ventriculomegaly patients [78-85].

Bielke et al. 1984 and Basser et al. 1985 introduced Synthetic Magnetic Resonance imaging (S-MRI), a quantitative imaging technique that measures inherent T1-relaxation, T2-relaxation, and proton density [86]. These inherent tissue properties allow synthesis of various imaging sequences from a single acquisition. Synthetic MR is a method which with a simple way calculates the volume of CSF located outside the ventricles in basal cisterns and brain cells. Virhammar et al. published 2018 research in which by using S-MRI they achieved to measure the ventricle volume changes after a shunt operation. Postopera-

Figure 4. An Evans index >0.3 is considered consistent with increased ventricular size



tive decrease in ventricle size is otherwise usually not detectable either by visual assessment or by measuring Evan's index in patients with iNPH [87].

RADSCALE

The most important part in diagnosis of iNPH is neuroimaging with the use of brain CT or MRI.

Common radiological criterion for iNPH is Evans ratio, which provides certain guidance, but is of limited value in differentiating iNPH from AD. The Evans ratio is the ratio of the maximum width of the frontal horns of the lateral ventricles and maximal internal diameter of the skull at the same level employed in axial CT or MRI images. This ratio varies with age and sex. An Evans index >0.3 is considered consistent with increased ventricular size [88] (figure 4).

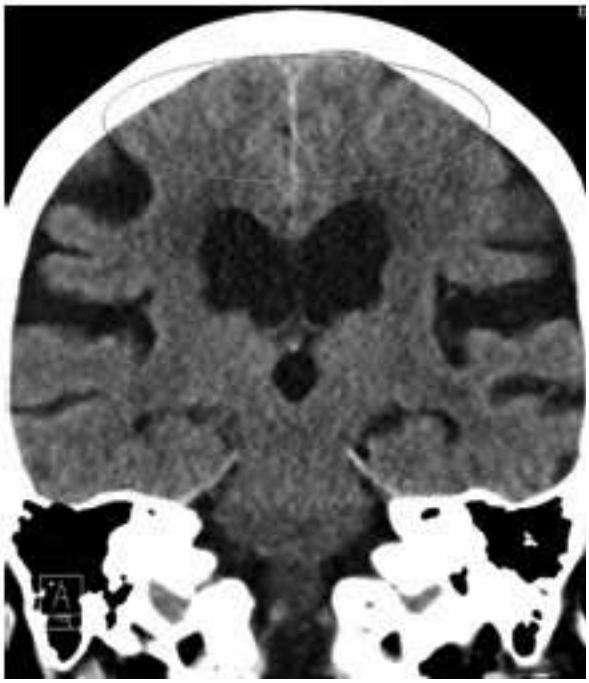
Tight high-convexity and medial subarachnoid spaces and enlarged sylvian fissure associated with ventriculomegaly, defined as disproportionately enlarged subarachnoid-space hydrocephalus (DESH) seem to be relatively good predictors of shunt surgery effect in iNPH. Focally enlarged sulci are seen in 25% of patients [89, 90] [91] [92] (figures 5 and 6).

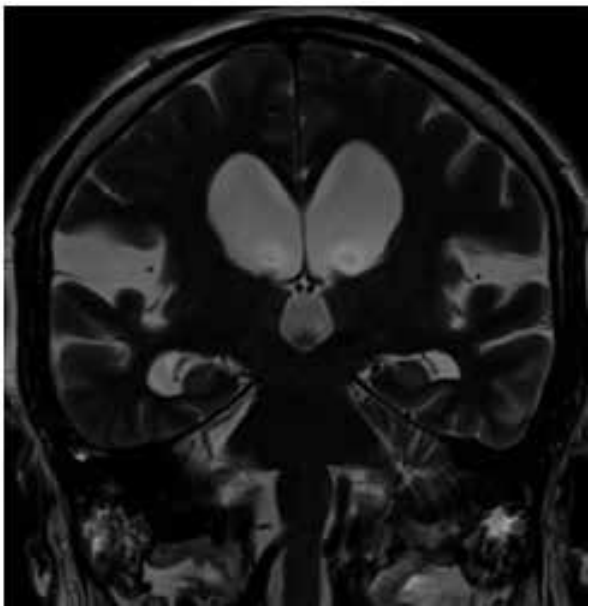
The corpus callosum angle has been proposed as a useful marker of patients with iNPH, helpful in distinguishing these patients from those with ex-vacuo ventriculomegaly. The most used cut-off is <90 degrees [93] [94] (figures 7 and 8).

Another radiological marker is the widening of the temporal horns not due to hippocampal atrophy [95] (figure 9).

All above radiological markers in combination with

Figures 5 and 6. Tight high-convexity and medial subarachnoid spaces and enlarged sylvian fissure associated with ventriculomegaly, defined as disproportionately enlarged subarachnoid-space hydrocephalus (DESH) seem to be relatively good predictors of shunt surgery effect in iNPH

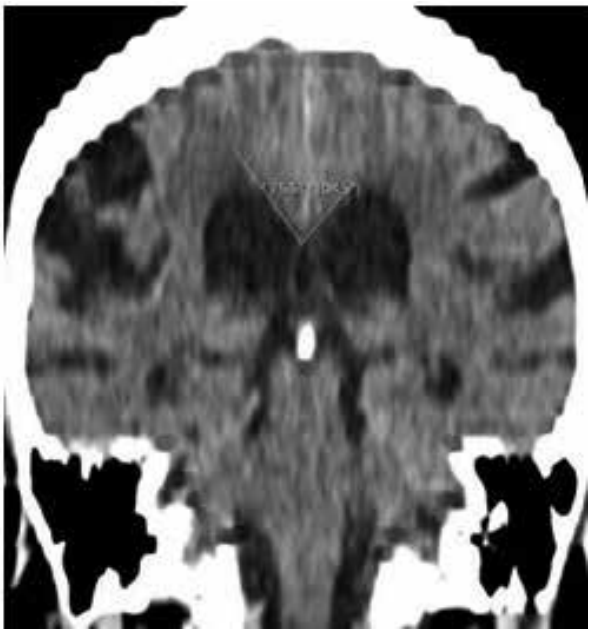




periventricular hypodensities (figure 10) are described in the Radscale (table 1). A patient with maximux score of 12 points gives clear importance for further investigation regarding the importance of a shunt operation.

A Radscale score≥8 points (maximum 12 points) suggest high probability of iNPH existence if typical symptoms are present [96].

Figures 7 and 8. The corpus callosum angle has been proposed as a useful marker of patients with iNPH, helpful in distinguishing these patients from those with ex-vacuo ventriculomegaly. The most used cut-off is <90 degrees



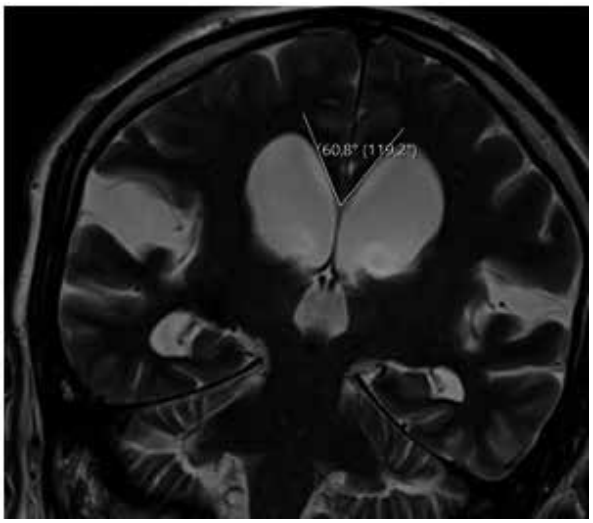


Figure 9. The widening of the temporal horns not due to hippocampal atrophy is another radiological marker for iNPH

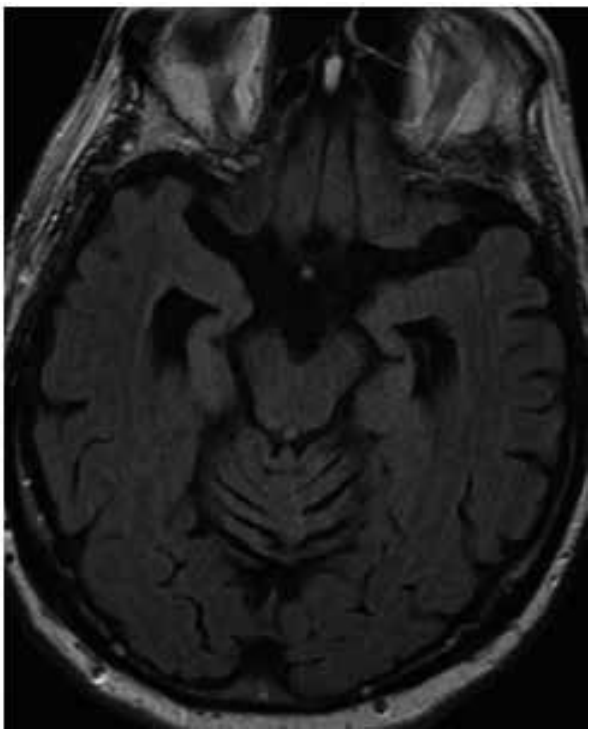
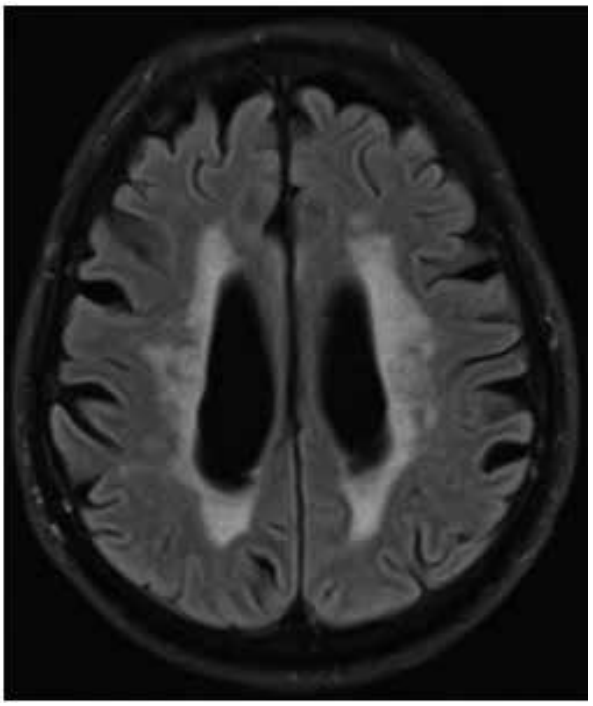


Figure 10. Periventricular hypodensities are usual radiological finding in patients with iNPH



Conclusion

INPH is a disease affecting elderly population, is difficult to differentiate from other common neurodegenerative diseases. A compilation of detailed medical history, meticulous clinical investigation, control of CSF biomarkers and dynamics, physiotherapist and occupational therapist evaluations and rigorous neuroradiological assessment could lead to identify the shunt-eligible iNPH patients easier.

Conflicts of Interest Statement

The authors declare no conflicts of interest.

Figures

All figures included in this manuscript are unpublished anonym radiological pictures from Andreas Eleftheriou personal digital archive.

Table 1. The Radscale: a scale for structured radiological assessment of patients with iNPH

Points	0	1	2
Evans Index	≤0,25	≥0,25-0,3	>0,3
Narrow Sulci	normal	parafalcine	vertex
Sylvian fissures	normal	widened	
Focally enlarged sulci	Not exist	exist	
Temporal horns	≤4 mm	4-<6 mm	≥6 mm
Corpus Callosal angle	≥90°	90° - >60°	≤60°
White matter lesions	Not exist	Punctate	confluent

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