From the Department of
Neurosurgery

Computerized analysis of intracranial pressure and cerebrospinal fluid dynamics in patients with idiopathic normal pressure hydrocephalus and positive clinical response to lumbar CSF drainage

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To my son and my beloved husband

Table of Contents Pag.

1 Introduction

In all ages of history, since antiquity [53] until today, we find that a very significant amount of anatomical, physiological, clinical and surgical studies had been dedicated to hydrocephalus. Likewise, we see that the history of neurosurgery had developed through the advances relating to the understanding and treatment of this pathology [110]. Maybe this is due to the fact that probably hydrocephalus is in general the most complete neurosurgical pathology, because apart of its etiological mechanism; its solution is essentially invasive or surgical. The 20th century brought technological advances that allowed us to explain pathophysiological mechanisms and established new diagnoses. In this sense, we encounter idiopathic normal pressure hydrocephalus (iNPH), which since its first

description in 1964 [1], [52], until the present, as we will see later, proposes a great number of questions. The etiology and the pathophysiological mechanism that explains it is still uncertain, which represents without a doubt a challenge for modern neuroscience. Fortunately, the continuous search for explanations has allowed to introduce in its study new diagnostic strategies, which have thrown light into the matter permitting the suggestion of new theories. This constitutes the reason for this dissertation. Due to the fact that these new diagnostic techniques and theoretical proposals are not definitive, some specialized centers in neurosurgery with research capabilities have directed resources to further study this disease. This is the case of the Neurosurgery Department of the Tübingen University Hospital (Germany), where under the guidance of Prof. Dr. med.

Martin Schuhmann exists a line of research about hydrocephalus and in particular about iNPH. The possibility to use the medical facility and the required technology, to have access to the patients, and the support of Professor Martin Schuhmann made of this work an enriching personal and professional experience.

This dissertation has two parts: The first part is a detailed bibliographical review about hydrocephalus and the most modern approaches to its understanding. This part has been written to offer to the reader the opportunity to learn about the most unknown disease treated by Neurosurgeons. It has to be considered as a separate effort outside of the usual thesis framework, which was created out of the enthusiasm of the author while trying to understand the phenomenon.

The theoretical first part begins with the general, pathophysiological aspects, diagnosis and treatment of iNPH. After that, the basic concepts, the classifications and demographic data will be presented. Then there will be an emphasis on pathophysiology, an attempt to establish differences easily recognizable among the current theories that try to explain it, a systematic comparison of them will be presented. In addition to the latter, it will be explained in detail the new proposal represented by the hydrodynamic theory [42]. As a contribution of this dissertation, this theory will be described and presented through diagrams. This part will end with the explanation of the current proposals for the diagnosis and treatment of iNPH.

The second part represents that investigative scientific part of the dissertation. Apart from a

clinical description of the patient cohort, the intracranial pressure (ICP) monitoring and cerebrospinal fluid (CSF) dynamics monitoring are the foundation of this work. It will be attempted to establish a relation between the pathophysiological proposal of the hydrodynamic theory and the results of ICP monitoring in order to predict the clinical improvement of our patients after draining the CSF with a shunt implantation. In short, and apart from the statistical results, this dissertation tries to be a theoretical and practical contribution in relation to the study and treatment of iNPH.

2 Part I - Review of Pathophysiology and Diagnosis/Treatment of iNPH

2.1 Cerebrospinal fluid (CSF)

The CSF is a clear and colorless fluid [101], which has mechanical protection, nutritive functions, transporting oxygen and glucose, immunological functions, transporting antibodies and immunoglobulin, and carrier functions, transporting and eliminating substances formed in the nervous system, like neurotransmitters, toxic or waste substances. Furthermore, recent studies indicate that CSF is not only an ultrafiltration of blood plasma, but that its production comes from energy dependent processes such as active transport [2]. Regarding its production, 80% of CSF is produced in the choroid plexus, while the remaining 20% is produced by the ependymal cells of the ventricles, the pial cerebral surface

and comes from the interstitial intracerebral space [112]. The total volume of ventricular and subarachnoid CSF ranges from 130 to 150 ml. The production rate is estimated to 0,30 - 0,40 ml per minute, which means up to 24 ml per hour or 500 ml per day [87]. The CSF pressure when measured by a lumbar puncture in lateral decubital position ranges from 60 to 150 mm of H2O (8-10 mmHg), the CSF intracranial pressure of a standing up person is close to zero or negative up to -10 mmHg [79].

Bulk flow theory

The classical theory that tries to explain the production, circulation and reabsorption of CSF, was proposed by Dandy. It has received since then many contributions [26] and thus it is today the most accepted theory, known as CSF bulk flow theory [22]. It sustains that at

the ventricular level the pressure is higher and then it decreases progressively along the subarachnoid space. For this reason and due to arterial pulsations of the choroid plexus, the CSF, which is produced in the latter, flows in caudal direction from its formation place (primarily the lateral ventricles) through the intraventricular foramina to the third ventricle [101]. Then it continues through the cerebral aqueduct to the fourth ventricle, from which it reaches through the fourth ventricle foramina (medial and lateral) the peribulbar and perispinal subarachnoid spaces. From these spaces it flows in rostral direction and through the tentorial notch reaches the basal and ambient cisterns, from which it ascends to the lateral and superior surfaces of both cerebral hemispheres. It is hypothesized that the arachnoid villi is the greatest absorption site. These villi gather to form the arachnoid

granulations, which calcify and grow in number and size with age. The CSF continues caudally through the central foramen of the spinal cord and along its subarachnoid space as well. According to this theory, the CSF absorption process in the venous sinuses happens when its pressure is greater than that of the sinuses. This could be expressed in a similar way to Ohm's Law (V=IR), where V (or voltage) would represent the difference between the pressures of CSF and the venous system, and it is this difference which causes the CSF to go into the veins; I (or current) expresses the velocity of the CSF flow, which in physiological conditions is equal to the velocity of its production; and R (resistance) represents the resistance to the CSF passing into the venous system, this resistance increases in cases where the CSF circulation is blocked, which in turn brings an increase of intracranial pressure

[112]. This theory was supported in the 1960s by studies that reported that those granulations could act as mechanic valves [116]. Additional support came from other investigations that made cisternographies with radionucleotides, in which 24 hours after applying radioisotopes to the CSF, it could be seen that the site of maximal accumulation of these radioisotopes was precisely the granulations [26]. However, recent studies that used radioactively marked albumin, reported that 90% of this protein was absorbed at the spinal canal, being maximally concentrated at the convexity of the sacrolumbar area 24 hours after the application. Therefore the CSF reabsorption mechanism proposed by the bulk flow theory would be incorrect [41], [43]. The belief that these villi act as unidirectional flow valves that absorb or transport CSF has been questioned as well, since there is no

anatomical or experimental evidence of this claim. Studies using electronic microscopy showed that each villus has a continuous fine membrane through which CSF flows, having a lineal increase rate, which depends on the CSF pressure (over 68 mmH_2O), but there was no valve system. Other studies using the same technology indicate that fine tubules covered with endothelium allow the CSF to flow indirectly toward the venous sinuses and when the venous pressure increases exceeding the CSF pressure, then compression at the level of the villi occurs that shut those tubules, which prevents blood extravasation from the veins to the subarachnoid space [101].

Modern theory of CSF

Recently has appeared a theory that tries to explain the CSF physiology called modern

CSF physiology and brain water [42]. It proposes that the CSF is produced and absorbed in any part of the central nervous system (CNS), where the former happens primarily at a production web in the choroid plexus and the latter at a minute web of capillary absorption in the subarachnoid space of the whole CNS. Additionally it establishes that the capillaries also produce an important quantity of interstitial fluid, which is approximately two times that of the CSF. Then, in case there is a fluid obstruction at intraventricular level, this fluid would substitute the CSF in the subarachnoid space. On the brain's external surface, there is between the interstitial fluid and the CSF a fast and random process of mixing and diffusion, which happens because of the cerebral arterial pulse. The transport of said mixture takes place because of the difference in its material

concentration gradient, for this reason it can happen in all directions. At intraventricular level, despite existing arterial pulsations, the dominant bulk flow is unidirectional, which goes from the ventricles to the subarachnoid space. This theory calls the mixture between CSF and interstitial fluid “brain water”, which is characterized by a low protein concentration (0,4% of the protein concentration in plasma) and a great chemical similarity between both fluids that makes difficult their separation. Because of the latter, the fluid of the interstitial space is defined as interstitial fluid and the external fluid of the brain as CSF. The filtration, absorption and homeostasis of brain water is maintained by a fluid exchange through the cerebral and arachnoid capillary membrane, which is governed by the Starling principle. This principle asserts that at each side of the capillary wall there are two

counteracting forces that maintain the balance regarding the fluid exchange. These two forces are the hydrostatic pressure, which is related to fluid filtration, and the oncotic or colloid osmotic pressure, which is related with fluid absorption. Due to the properties of the arteriole and the cerebral capillary, there is a fluid homeostatic balance that helps to maintain a physiological and positive intracranial pressure. The close relationship between production and absorption of both CSF and interstitial fluid occurs at the cerebral capillaries, in a similar way as it happens in all the other capillaries of the body, i. e., through the active absorption of proteins and other macromolecules from the plasma to the CSF.

2.2 Hydrocephalus

Hydrocephalus is recognized as a pathological entity since the fifth century B. C. Its name

comes from the greek words ὕδωρ (water) and κεφαλή (head), which would mean water inside the head, although it is not referring to water but to cerebrospinal fluid (CSF) [110]. It is traditionally defined as the excessive accumulation of CSF in the ventricular system, which brings as a consequence its abnormal dilation. Due to direct brain monitoring and to gradient pressure analysis using MRI and CT appeared a new concept of hydrocephalus [44], [45], which asserts that because of the brain tissue plasticity, the brain responds to local forces (for example, pressure changes) with displacement, deformation and by being remodeled. This remodeling of the brain parenchyma and the CSF space is what is defined as hydrocephalus [25]. The ventricles enlargement at the expense of restricting the subarachnoid space indicates that there is an

increased regional force from the ventricles toward the subarachnoid space. The pressure gradient that appears is called transmantle pulsatile stress or transmantle pressure. This stress is a dynamic phenomenon that acts through time, depends on the pulse waves, and is the only possible force that could be responsible for the brain tissue and the CSF space deformation [47]. It also asserts that this stress can be reversed or reduced through CSF shunting and that the subsequent normalization of the spaces involved indicates that the transmantle pulsatile stress really exists.

Classification

Hydrocephalus is classically classified in two big groups, obstructive and non obstructive Hydrocephalus. Non obstructive Hydrocephalus may theoretically be caused by

an increased CSF production or due to an atrophy process of the brain parenchyma, where a passive enlargement of the ventricles occurs. This last kind is also called Hydrocephalus ex vacuo, but it should be noted that strictly speaking from a pathophysiological point of view, this is not a real hydrocephalus. Obstructive Hydrocephalus is subclassified in communicating and non communicating. Communicating hydrocephalus is present when the CSF flow is free inside and out of the ventricular system but is diminished or obstructed everywhere beyond the ventricular outlets, classically believed to be obstructed at the reabsorption level, i. e. at the level of the arachnoid villi or granulations, along the superior sagittal sinus [38]. Non communicating cases are those where we find obstruction evidence of the fluid flow inside or

at the outlet of the ventricular system. The hydrodynamic concept also classifies the disease in two groups: acute and chronic hydrocephalus [42]. We speak of acute hydrocephalus when there is a new obstructive process of the intraventricular flow or outflow. Chronic hydrocephalus is subdivided in two kinds: communicating hydrocephalus and chronic obstructive hydrocephalus. Restricted arterial pulsation and increased pulse pressure of the brain capillaries maintain the ventricles enlargement in the two kinds of chronic hydrocephalus. This understanding proposes as main cause of chronic hydrocephalus a decreased intracranial compliance and not CSF malabsorption.

2.3 Idiopathic normal pressure hydrocephalus (iNPH) or idiopathic adult hydrocephalus syndrome (IAHS)

The classic view defines it as a communicating hydrocephalus [49], which presents normal CSF pressure levels. It is characterized by being chronic and presenting the symptomatic triad that includes gait disorders, dementia and urinary incontinence, which can be reversible under treatment. Continuous monitoring of intracranial pressure (ICP) in these patients has allowed to demonstrate that those „normal“ pressure levels could present aleatory elevations. Because of this, the better name should be “idiopathic adult hydrocephalus syndrome”, however the denomination “idiopathic normal pressure hydrocephalus” continues to be used because of its historical tradition.

The hydrodynamic point of view proposes a new definition of iNPH. According to this theory, this kind of hydrocephalus is chronic and communicating, in which there is a deformation of the brain and the CSF space. The ventriculomegaly is present with a normal or almost normal intracranial pressure. All of this is related to a decreased intracranial compliance, which causes an increased intracranial pulsatility which effects ventriculomegaly.

Etiology

Etiologically it could be idiopathic (65%) or secondary (35%) [57], the latter being associated to states after subarachnoid hemorrhage, cranioencephalic trauma, neoplasia, postsurgical states, congenital malformations, and inflammatory diseases of the brain or the meninges, meningeal

carcinomatosis being included [94]. The precise triggering or etiological factor has not been elucidated. Age related deep white matter lesions have been described as a possible etiological explanation of iNPH [65]. There is a second hit theory [12], which states that iNPH could begin in infancy as an external hydrocephalus that would be followed in old age by different grades of deep white matter ischemia. This would produce a decrease in the traction force of the ventricles. However, according to this theory, the deep white matter ischemia is a cause of iNPH but not the only one [14]. Other studies show that in some cases the ventriculomegaly exists 20 years before the patient develops the symptomatic triad of iNPH [13]. Another pathological entity that supports the chronic and progressive aspects of hydrocephalus, which begins in childhood and becomes symptomatic in

adulthood, one of its signs being adult macrocephaly, is the so called LOVA (long-standing overt ventriculomegaly of the adult) [83], [84].

The hydrodynamic theory suggests that communicating hydrocephalus has a direct relation with the vascular disease, which would bring a decreased arterial compliance and an increased capillary pulse pressure [42]. This vascular disease is in turn associated to multiple factors such as old age, arterial hypertension, brain arteriosclerosis, diabetic microangiopathy, and arterial ectasia among others. Nevertheless, there remain still many doubts about the predisposing and/or unleashing factor, since not every patient with vascular comorbidity develops iNPH in old age. However it is true that most patients, who are diagnosed with the disease, have one or

some of these vascular factors in their personal history.

Epidemiology

Regarding its epidemiology, there are no world statistics. However, a multicentral and prospective study carried out in Japan with a sample of 117 patients, whose average age was between 74 years old (+/- 5) and 58% were male [47]. Another study carried out in Norway encompassing 220 000 persons, reported a prevalence of 21,9 and an incidence of 5,5 in every 100 000 persons, both of which increased with age. Besides it suggested that those results should be considered as minimal estimates and that its presence is not associated neither to race nor gender [15]. Other studies in small populations indicate that despite being underdiagnosed, because there is no consultation when its

symptoms are present, the disease appears in more than 0,40% of the general population older than 65 [16] and represents between 1 to 6% of all dementias [109].

Pathophysiology: Classic theory

Pathophysiologically its true mechanism remains unclear and because of this there is a constant debate, with different theories being proposed trying to explain it. The fact that this CSF reabsorption decrease and its subsequent accumulation in the ventricular system do not generate chronic intracranial hypertension [3], [44], but chronic and progressive ventriculomegaly, was explained by Hakim by applying the law of Pascal regarding fluids contained in an elastic compartment. According to the hydraulic press effect [38], [42], [49], the intracranial pressure (ICP) is a phenomenon that depends on

various physiological factors: first, the arteriole-capillary blood pressure, which through vasoconstriction changes manages to modify the ICP and the CSF pressure; second, the venous pressure, which regulates the intracranial blood volume; third, the brain parenchyma, which is comparable to a sponge made of viscoelastic material [78], whose cells are full of fluid (extracellular fluid and brain blood included) and its progressive deformation is attributed to the collapse of parenchymal veins; and fourth, some pathological element, which is not always present. He also stated that in order to evaluate the intracranial pressure changes, it has to be taken into account that in physiological conditions there is a balance between CSF, brain volume, vascular volume and the strength of the arteriole-capillary vessels. In the case of iNPH, he proposed that

the existence of a partial block regarding CSF circulation would produce hydrocephalus. According to this theory there are two phases in the disease. In the first one, there is a transitory period of intracranial hypertension, which comes as a result after a pressure gradient between the ventricular system and the subarachnoid space is established. Thus, using the equation (Force = Pressure x Surface), it explains the appearance of ventriculomegaly. This pressure increase persists until the formation and absorption of CSF reach a balance. Presumably this is due to the fact that brain arteriolo-capillary pressure, intracranial blood volume and CSF pressure equilibrate each other in this pathological condition. In the second phase the ventriculomegaly persists, therefore the intracranial pressure decreases due to the fact that a smaller CSF pressure is being exerted

on a bigger contact surface. Despite a normalization of CSF pressure, the ventriculomegaly remains, and therefore the clinical symptomatology remains as well. When there is a new increase of CSF pressure, the ventriculomegaly increased again until reaching a new equilibrium point [20], [93].

Definition of terms

Before going on and with a didactical end in mind, it is necessary to define the following neuro-hemodynamic concepts, which are essential in order to understand the hydrodynamic theory, which will be presented immediately afterward.

Pulse Pressure: is defined as the difference between systolic arterial pressure (SAP) and diastolic arterial pressure (DAP). It is expressed in mmHg and is considered an

indicator of arterial distensibility. There are studies that demonstrate that the pulse pressure increases with age, both in men and women, simultaneously with SAP increase, mainly in the population older than 60 [5].

Perfusion pressure (PP) and cerebral perfusion pressure (CPP): the perfusion pressure of any tissue is equal to the difference between mean arterial pressure (MAP) and the venous pressure (VP); PP = PAM - VP. Because the venous pressure is similar or slightly lower than the ICP, and that at intracranial level the dynamics of vascular flow is closely related to it, the CPP is defined as the difference between mean arterial pressure and intracranial pressure; CPP = MAP – ICP [112]. The greatest threshold value which is accepted for adults ranges between 60-70 mmHg [21].

Vessel distensibility: it is defined as the vessel's capability to distend because of pressure changes, accompanied by a decreased resistance to the fluid flow through them. It is expressed in the following way: distensibility = volume increase / pressure increase x original volume. The distensibility is inversely proportional to vessel Elastance [51].

Elastance: generically it is define as a measure of the tendency that a structure with elastic properties has to return to its original form once the deforming force has been removed. In medical physiology it usually refers to the measure of the tendency of a hollow viscus (e.g. urinary bladder or blood vessel) to return to its original shape once the force that distends or compresses it disappears [103].

Intracranial compliance (C): also called space adaptability or volumetric distensibility, is the brain capability to adapt to changes in volume (Vd) inside the cranium in order to compensate intracranial pressure changes (Pd) [75]. In analytical terms, it is defined as the relation between the received intracranial volume difference and the intracranial pressure difference that said volume exerts: C = Vd / Pd [28]. Regarding the intracranial dynamics, it must be said that the compliance is inversely proportional to pulse velocity. While the transmission of pulse pressure in a non adaptable cavity takes place at the speed of sound, the transmission velocity of intracranial pulse pressure is much more slower. This is due to the fact that both intracranial veins and spinal thecal sac have a high space adaptability or compliance [42].

Vessel capacitance: also called vessel adaptability or vessel compliance is defined as the total amount of blood which can be stored in the blood vessels from a specific part of the circulation for every mercury millimeter of pressure. This means that the greater the vessel adaptability or capacitance is, the easier it will be that the vessel distends because of a pressure increase. Capacitance = vessel volume increase / vessel pressure increase [51].

Vessel impedance (Z): it is the hindrance that the arterial tree system of ramifications (hydraulic) presents to both the establishment of blood flow and its pressures. Said in another way, it is the opposition to the circulation of pulsatile flow. Impedance describes through its components the state of circulatory ways and the coupling of fluid and pressure between

these ways and organs. This includes viscosity effects, ramifications and angulations, changes in diameter, and arterial elasticity (distensibility). Therefore it helps to evaluate the physiology of the circulatory system. In analytical terms, it can be expressed as the magnitude (Z) that establishes a relation or quotient between tension (V) and current intensity (I): $Z = V / I$ [88].

Monro-Kellie Doctrine [59], [81], [114]: it asserts that the cranial cavity is a semi-closed and rigid space, which contains a constant volume in each moment of the cardiac cycle. The total intracranial volume (V_c) is composed by the combination of the following four elements: first, the brain parenchyma (+capillary blood) ($V_{cerebral}$), which represents approximately 80% of intracranial content; second, the CSF (V_{CSF}), which represents

nearly 10%; third and fourth, arterial ($V_{arterial\ blood}$) and venous blood ($V_{venous\ blood}$) respectively, both of which represent the remaining 10% of intracranial content. These four elements are encircled by the dura mater, which is of low elasticity and is in turn covered by a rigid container, i.e., the cranium. Analytically it is expressed in the following way: $V_c = V_{cerebral} + V_{arterial\ blood} + V_{venous\ blood} + V_{CSF}$. Given the case that one of this components increases in volume, the others will be affected and therefore have to adapt. This they accomplish by structural alteration in order to compensate for the lack of space, which forces them to diminish their volume inside the cranium (displacement). The compensatory displacement of the affected components is only temporal, but if the alteration continues they will be functionally affected. In addition to this, there would be an

intracranial pressure increase, due to the fact that fluids are incompressible. Recently, some authors have indicated that the Monro-Kelly hypothesis lets out of consideration the material properties of the brain. According to this mathematical model of hydrocephalus [78], the severity and chronicity of physiological and neurological changes could be determined by these properties.

Windkessel effect: it is the arterial tree system capability to transform the pulsatile flow of the central arteries in a continuous flow during the diastole, which is required by the peripheral tissues. As we well know, the great arteries have two main functions, which despite being different are closely related and regulated between each other/them. The first one is called conduction function, which is related to the arterial pressure static component (mean

arterial pressure). They accomplish this function, because they constitute low resistance ducts of blood distribution, which allow them to deliver an adequate blood supply to the peripheral organs. The second one is called damping function, which is related to the pulsatile component (pulse pressure), i.e., they damp the pressure oscillations caused by the intermittent nature of the ventricular ejection [71], [82], [86]. Due to this damping function, the great arteries store a part of the systolic volume during the systolic ejection (in normal conditions nearly 60%), which is returned during the diastole, losing 15% of stored energy as heat or dissipated energy. The latter is denominated Windkessel arterial effect.

Stroke volume (SV) [96]: it is the volume of blood pumped from a heart ventricle with each

beat. It can be expressed as the substraction of the end-systolic volume (ESV) from the end-diastolic volume (EDV). SV = EDV - ESV.

CSF stroke volume: it is defined as the CSF mean volume that flows through an encephalic cavity during both the systole and diastole [97]. If the cavity is the ventricle, it is called ventricular CSF stroke volume and if it is the aqueduct, then it is called aqueductal CSF stroke volume.

Pathophysiology: Hydrodynamic theory

Continuing with the pathophysiology, there is another explanation, which tries to make clear the pathophysiological origin of iNPH. It is put forward by the so called “hydrodynamic theory” [42], which was developed by Greitz on the basis of MRI observations and measurements of arterial, venous and CSF pulsatility [44].

According to Greitz et al. [46], there are volumetric changes in physiological conditions, in which the features of cerebral expansion could be inferred through the Monro-Kellie doctrine modified by Weed [114]. They say that total expansion has two components, i.e. arterial and brain expansion, which are difficult to differentiate. On one hand, the intracranial arteries expansion during the systole is compensated by the proportional CSF outflow through the foramen magnum and venous blood outflow to the dural venous sinuses. On the other, the brain expansion takes place when the intracranial pressure is lower than the CSF spinal pressure and when there is a simultaneous increase of total CSF intracranial volume. This is possible due to arterial expansion, which is responsible for the main part of the cervical CSF systole, because it creates space after its conclusion. The brain

expansion comes from an increase in brain volume, which during the late systole compresses the ventricular system and mainly the veins. Strangely, while the blood is still inside the arteries, the CSF plunges through the foramen magnum into the cranial cavity. The anatomo-functional explanation of this comes from the fact that said arterial systolic expansion compresses the venous outlets of the bridging vein, causing a systolic flow at the venous sinuses. Functionally, it could be said that the dural venous sinuses are located outside the cranial cavity, which causes compression at the venous outlet. Because of the latter the fall of pressure in this location is maximal. At the same time there is a recirculating CSF flow, which is caused by intracranial extracerebral arterial pulsations. According to the Law of Pascal, the increased CSF pressure caused by the pulse wave

entering into the cranium is distributed across the entire intracranial space, which equilibrates the pressure difference. Despite of this, there appear new temporal pressure gradients during each cardiac cycle; therefore the flow effects produce intracranial fluid displacement [42].

This theory proposes that iNPH or communicating hydrocephalus is characterized by a disorder of the intracranial pulsations complex harmony, i.e. between the brain arterial pulse and the CSF pulsatility, due to a decreased intracranial compliance. According to this reasoning, a chronic reduction of intracranial compliance restricts arterial expansion, which unleashes a series of effects on intracranial vascular and CSF dynamics, which in turn cause normal pressure ventriculomegaly, and also perpetuate and produce ulterior compliance decreases. In this

way a vicious circle is formed. In relation to this theory, it is pertinent to recall that in recent animal experiments with kaolin injection in the basal cisterns, it was observed a decreased intracranial compliance of the basal arteries and a direct interference with CSF pulsatile motion at that level, which increased the CSF pulsatility and produced ventriculomegaly [70], [113].

The main effects caused by decreased intracranial compliance are the following: decreased intracranial stroke volume, increased CSF pulse pressure, decreased brain blood flow, and lastly decreased intracranial arterial expansion. In turn, this diminished arterial expansibility has the following consequences: first, increased vascular impedance; second, breakdown of the Windkessel effect along the main vessels; and third, increased arterial pulse wave. As it

will be explained later, all these effects have as final consequence ventricular enlargement and diminished blood brain flow.

In order to make this work an explanatory tool of this pathophysiological mechanism, the effects just mentioned will be treated in detail. As it will be explained in what follows, these effects are closely related between them, having all of them the same starting point, and having intermediate and final mechanisms in common as well. Because of this, there are pathological positive feedback processes that form a vicious circle, which would explain the chronic and progressive aspects of iNPH. Additionally, we can see that through diagnostic methods it is possible to confirm the occurrence of these pathological effects.

Decreased intracranial compliance causes: a decreased intracranial stroke volume, an increase of CSF pulse pressure, a diminished

expansion of intracranial arteries, and a diminished brain blood flow. In patients with communicating hydrocephalus, the intracranial stroke volume is diminished in approximately 50%. This is known because of studies made with flow-sensitive MRI [56], which demonstrated that in these patients the stroke volume at the craniocervical-junction is diminished in nearly 50% and it is also diminished in a third at the intracranial venous sinuses. The diminished intracranial ejection volume produces, on the one hand, a diminished brain blood flow, which in turn diminishes the transcapillary pressure difference between blood and tissue, conducing to a diminished fluid exchange through the capillary wall. In this way the CSF absorption at the capillary level is affected. On the other hand, the diminished intracranial compliance directly increases the CSF pulse

pressure (approximately 6 times) [30]. These two main effects, i. e. diminished intracranial ejection volume and increased CSF pulse pressure, directly diminishes in one order of magnitude the intracranial compliance, which is the proportion or relation between volume change and pressure change [42]. In this way the first positive feedback circle is formed, which helps to perpetuate the mechanism that diminishes the intracranial compliance. Additionally the combination of these two effects brings forth an increased transmission pressure from the CSF to the vascular system, which also has a direct diminishing effect on the CSF absorption at the brain capillary. The diminished CSF absorption, which is the consequence of a flow and pressure disorder, can be seen through a lumbar infusion test with intracranial pressure monitoring, in which we observe an increased resistance of the

CSF outflow (Rcsf) [115]. The diminished intracranial compliance causes in turn a diminishing of the intracranial arteries expansion, which will unleash a series of more complex mechanisms that will be explained later on. One of them is an increased intracranial vascular impedance. This increases the resistance to the pulsatile flow which results in a diminished blood flow average and also a diminished flow of the whole brain blood. As it was already mentioned, the decrease in blood brain flow diminishes the CSF absorption at the brain capillary [42]. (See diagram 1).

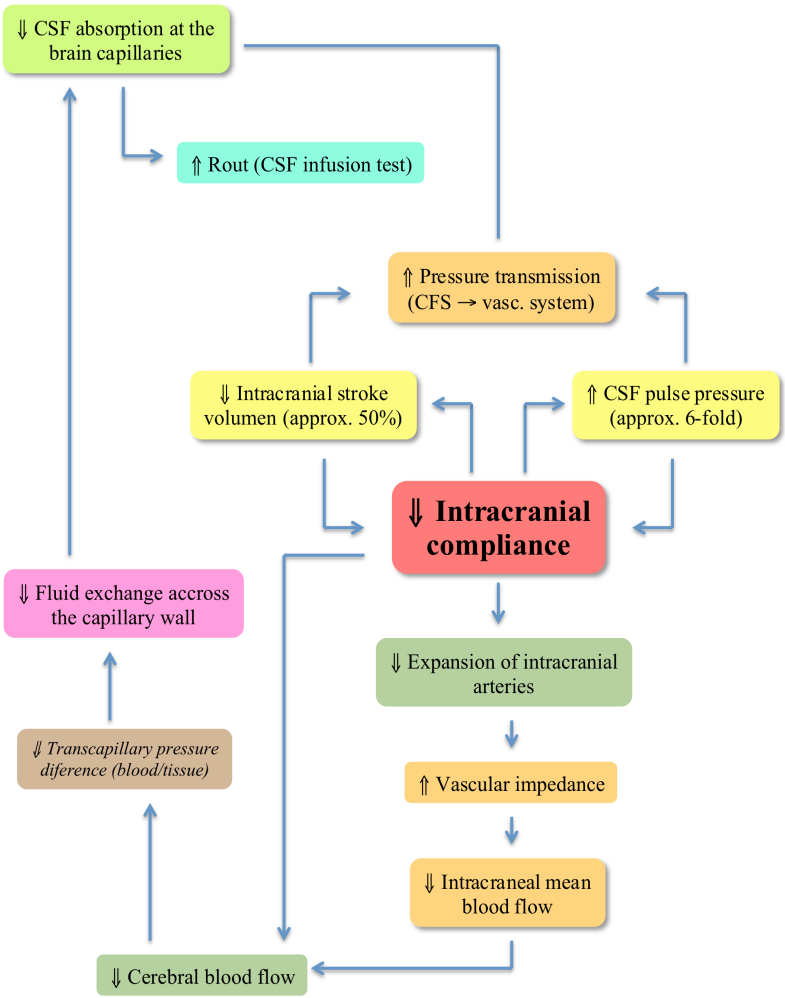
The intracranial compliance decrease causes a diminished arterial expansion, which produces, on the one hand, the breakdown of the Windkessel mechanism along the great vessels at the base of the cranium, and on the other, the arterial pulse wave increase. The

Windkessel mechanism breakdown decreases the arterial diastolic flow, which in turn increases the pulsatility of intracranial arteries. The latter can be seen through the transcranial Doppler, where the pulsatility index would appear increased, i. e., bigger than one. The arterial pulsatility increase disrupts the synchrony between the arterial, venous and CSF pulses, resulting in an increase of the parenchyma capillaries pulsation [44]. This increase raises the brain pressure in comparison to the subarachnoid space, which brings about a decrease of the pressure difference between the vascular system and brain tissue. The latter allows the transmission of the systolic pressure from the capillary to the brain tissue. The wave increase of the intracranial arterial pulse happens due to the fact that the arteries cannot expand and because of this the buffer effect decreases,

which is responsible for softening the arterial pulse wave.

The decrease of arterial expansion decreases the CSF volume conduction, which bypasses the brain capillary, i.e., the one which directly goes from the (expanding) artery to the (compressed) bridge veins. The energy, that is generated here, creates a forced pressure and transmission volume of the pulse wave from the artery to the capillary and brain tissue. Subsequently the brain capillary absorbs this hydraulic energy of the pulse wave, resulting in an increase of the brain capillary pulsations.

Diagram 1


⇓ CSF absorption at the brain capillaries
⇑ Rout (CSF infusion test)
⇑ Pressure transmission (CFS → vasc. system)
⇓ Intracranial stroke volumen (approx. 50%)
⇑ CSF pulse pressure (approx. 6-fold)
⇓ Intracranial compliance
⇓ Fluid exchange accross the capillary wall
⇓ Expansion of intracranial arteries
⇓ Transcapillary pressure diference (blood/tissue)
⇑ Vascular impedance
⇓ Intracraneal mean blood flow
⇓ Cerebral blood flow

Later on the brain capillary absorbs this hydraulic energy of the pulse wave, which results in a brain capillary pulsations increase. In physiological conditions, that energy is absorbed by the artery and not the capillary. In the end, this also leads to the transmission of the systolic pressure from the capillary to the brain tissue. As it was already explained, the latter is also a consequence of an increased intracranial arterial pulsatility, which in turn is a consequence of the breakdown of the Windkessel mechanism and a decreased arterial diastolic flow. Additionally, this increase of the intracranial arterial pulsatility contributes to an increase of the arterial pulse wave, so that it reinforces the increase of the capillary pulsatility of the brain parenchyma. As it was already said, both the pulsatility increase of the brain capillaries and the pulse wave increase at the artery are responsible for

the transmission of the systolic pressure from the capillary toward the brain tissue. This systolic pressure transmission causes a compression increase of the vessels along their course inside the subarachnoid space, which produces a compression of the vessel capacitance and an increase of venous brain pressure. The reduction of vessel capacitance directly decreases the brain compliance and additionally increases vascular resistance, which is followed by a decrease of the brain blood flow. The increase of vascular resistance can be shown as a small increase of the CSF mean pressure, which is not meaningful in relation to intracranial pressure in general, given the fact that the CSF total pressure is normal or almost normal in communicating hydrocephalus. The increase of brain venous pressure is followed by a decrease of perfusion pressure and consequently by the

decrease of brain blood flow [104]. On the other hand, a decreased compliance joined by a decreased brain blood flow disrupts the normal autoregulation mechanisms by which the blood vessels regulate the flow. As a consequence a compensatory mechanism consisting in a dilation of the brain arterioles, takes place. This compensatory response is inefficient, because instead of increasing the blood flow, it generates an increased local pressure. This last effect can be seen during intracranial pressure monitoring through the increased appearances of A and B high pressure weaves of vascular origin [42]. (See diagram 2)

A decreased intracranial compliance causes, as was already mentioned, a decreased arterial expansion, which ends up breaking down the Windkessel mechanism. This break down diminishes the diastolic arterial flow,

augments the intracranial arterial pulsatility and capillaries pulsations. All of these causes the expansion of the brain parenchyma [41], [44], [46]. This expansion occurs predominantly (as a vector force) centripedally inside toward the ventricles, since the inner surface of the brain (ventricular surface) is much smaller than its outer surface area, augmenting the intraventricular pulse pressure. The latter produces an increased transcranial pulsatile pressure. This increase is a consequence of the brain autocompression against the ventricular system during each systole, due to the fact that the brain parenchyma has a high plasticity while the CSF is incompressible. If we apply the latter to the Law of Pascal, it is assumed that the counterforce produced from the ventricles equals the force of brain expansion. As it was already mentioned, due to its high plasticity,

the brain does not regain completely its pre-systolic volume during each diastole. This produces a cumulative effect of brain compression during each systole, which over time would explain a progressive and compensatory dilation of the ventricles. Some studies claim that a sign of the decreased compliance and of the increased pulsatile transcortical pressure is the progressive ventricular size enlargement [100].

The increase of the pulsatile transcortical pressure produces a compression of the intracranial vessels capacitance (brain and cortical veins, and brain capillaries), which as was already mentioned diminishes directly the intracranial compliance. Coming back to the sequence of the pathophysiological mechanism, we recognize that an increased intraventricular pulse pressure causes,

besides ventriculomegaly, two additional effects.

The first one consists in a hyperdynamic flow of CSF at the aqueduct. Studies made with Cine phase-contrast MRI reported that in the cases of patients with symptomatic iNPH, the CSF ejection volume at the aqueduct level increases in time if the patient does not receive a CSF shunt [97], which would speak in favor of the mechanism being described. The second effect is a direct result of a decreased intracranial compliance, being therefore a way in which this mechanism suffers a positive feedback. It is important to mention that the decrease of the supratentorial compliance is greater than the one of the infratentorial compliance. This happens because the infratentorial space is closer and in direct communication to the spinal dural sac, which has a high compliance and in turn helps

to compensate the compliance decrease at this level.

This would explain the reason why in communicating hydrocephalus, the ventriculomegaly is lesser or even does not exist under the tentorium [42]. It must be said that in spite of the decrease of brain blood flow, which produces a diminished CSF absorption, the hydrodynamic theory attributes the ventriculomegaly to the consequences of the decreased compliance and the increased intraventricular pulse pressure. However, it is not clear if this diminished absorption at the brain capillary level plays any role in regard to the ventricular enlargement, which is what has been claim for the last five decades. (See diagram 3).

In short, in order to stress the role of the vascular disorder at the pathophysiological origin of iNPH, the hydrodynamic theory

proposes the following terms: “restricted arterial pulsation hydrocephalus or increased capillary pulsation hydrocephalus”. On the other hand, this pathophysiological mechanism would explain the reason why there is temporary clinical improvement after the CSF evacuation during the diagnostic lumbar puncture and also why there is permanent clinical improvement after the CSF shunt, after the endoscopic ventriculostomy of the third ventricle, and after the decompression of the posterior fossa in those cases in which hydrocephalus is caused by the obstruction of the CSF pulsatile flow at the level of the foramen magnum.

Diagram 2

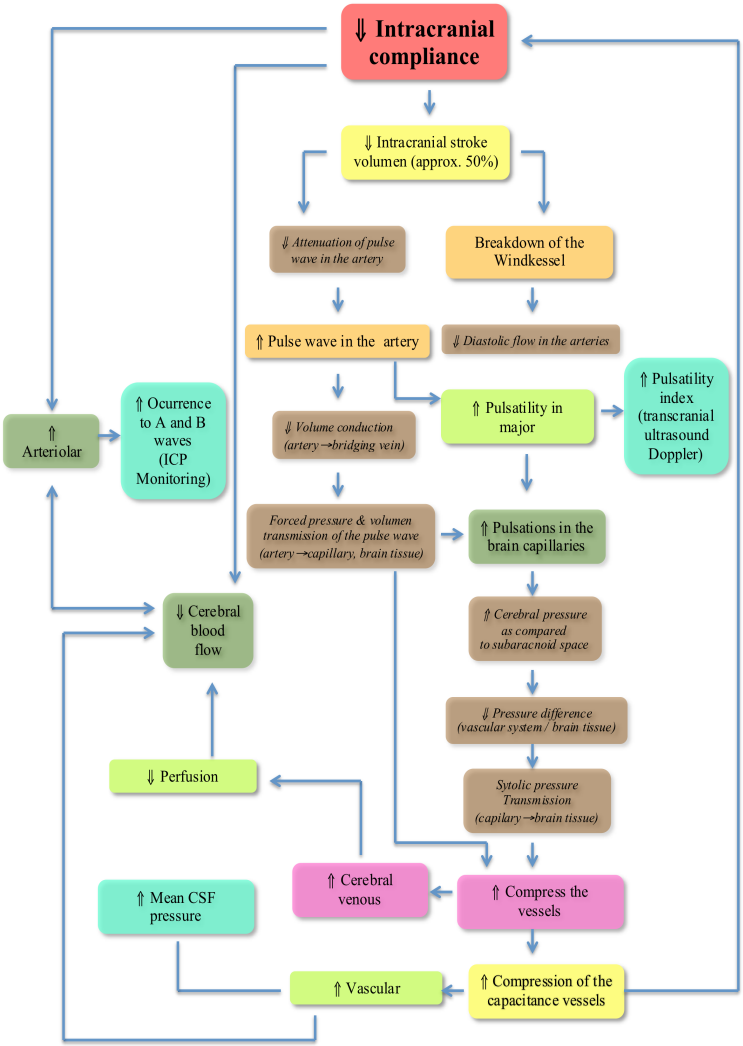
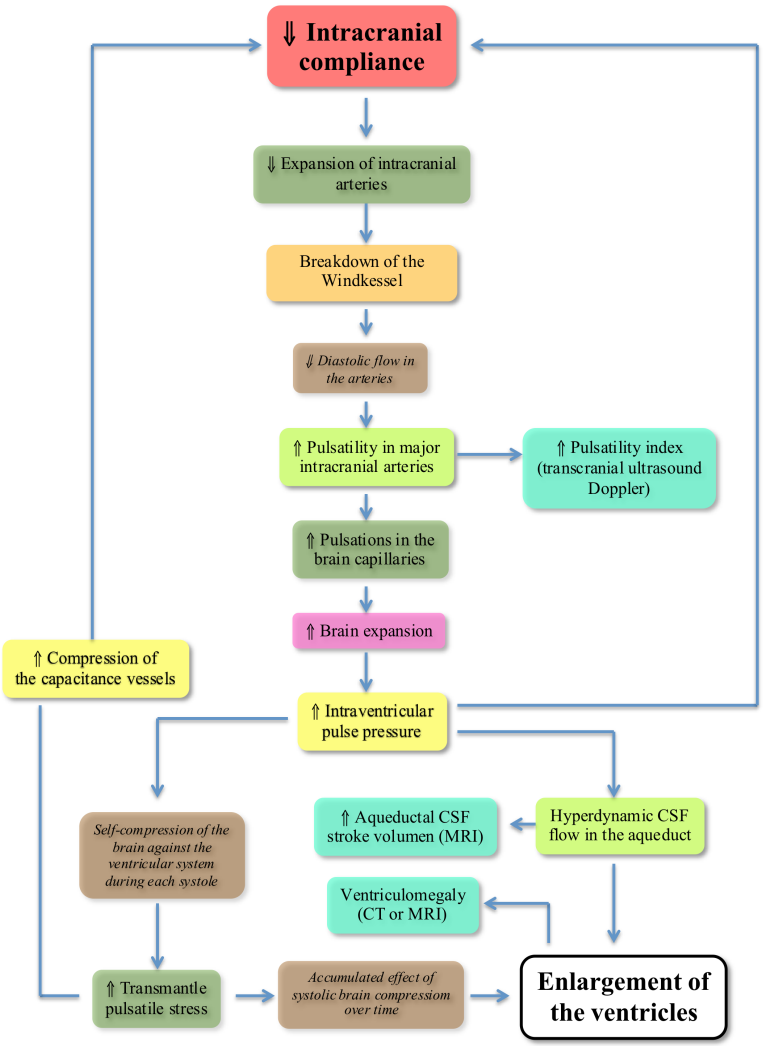

⇓ Intracranial compliance
⇓ Intracranial stroke volumen (approx. 50%)
⇓ Attenuation of pulse wave in the artery
Breakdown of the Windkessel
⇑ Pulse wave in the artery
⇓ Diastolic flow in the arteries
⇑ Arteriolar
⇑ Ocurrence to A and B waves (ICP Monitoring)
⇓ Volume conduction (artery→bridging vein)
⇑ Pulsatility in major
⇑ Pulsatility index (transcranial ultrasound Doppler)
Forced pressure & volumen transmission of the pulse wave (artery→capillary, brain tissue)
⇑ Pulsations in the brain capillaries
⇓ Cerebral blood flow
⇑ Cerebral pressure as compared to subaracnoid space
⇓ Pressure difference (vascular system / brain tissue)
⇓ Perfusion
Sytolic pressure Transmission (capilary→brain tissue)
⇑ Mean CSF pressure
⇑ Cerebral venous
⇑ Compress the vessels
⇑ Vascular
⇑ Compression of the capacitance vessels

Diagram 3


⇓ Intracranial compliance
⇓ Expansion of intracranial arteries
Breakdown of the Windkessel
⇓ Diastolic flow in the arteries
⇑ Pulsatility in major intracranial arteries
⇑ Pulsatility index (transcranial ultrasound Doppler)
⇑ Pulsations in the brain capillaries
⇑ Brain expansion
⇑ Compression of the capacitance vessels
⇑ Intraventricular pulse pressure
Self-compression of the brain against the ventricular system during each systole
⇑ Aqueductal CSF stroke volumen (MRI)
Hyperdynamic CSF flow in the aqueduct
Ventriculomegaly (CT or MRI)
⇑ Transmantle pulsatile stress
Accumulated effect of systolic brain compressiom over time
Enlargement of the ventricles

Clinical diagnosis

In relation to clinical diagnosis, iNPH is characterized by the Hakim-Adams typical symptomatic triad [49]. The classic triad consists of: walking disorders, cognitive disorders and urinary incontinence. These symptoms usually appear in the order in which they were named. This is the most frequent way in which the sickness appears, but there are some cases in which this sickness presents itself in a way that does not follow the classic pattern [39]. This symptomatic triad is not pathognomonic for iNPH, given the fact that it appears in other subcortical dementias, like those with a vascular origin, and the Alzheimer disease, which is cortical dementia. The clinical forms are the following: typical, atypical, incomplete and mixed [89], [90]. Some series show that these patients have a worse response in relation to a CSF shunt and

in the case of a clinical improvement, this happens only regarding the walking disorders and urinary incontinence [98], [111].

In relation to the presentation frequency of clinical symptoms, the complete triad appears in approximately 50% of the patients. Walking disorders is the most frequent clinical manifestation, because as the only symptom it is present in approximately 10% of the patients; as a symptom associated to cognitive disorders is present in approximately 30% of the patients; and as a symptom associated to urinary incontinence it is present in approximately 7% of the patients. Likewise, we know that in order of frequency follow the cognitive disorders, which are present as the only symptom of the disease in approximately 2% of the patients, and as an associated symptom to urinary incontinence in approximately 3% of the patients. At last, the

urinary incontinence appears as the only symptom in approximately 0,3% of the patients [23], [91]. Traditionally, the iNPH symptomatology has been related to the alteration, first morphological, and then functional of the fascicles of the periventricular white matter (corona radiata). This alteration is caused by ventricle enlargement, which even with a normal pressure distends the corona radiata. This explains the fact that iNPH symptomatology is reversible by CSF shunting. In spite of this, it is known that on late stages of the disease, there is a no return point, i. e. despite surgical treatment, the patients highly suspected of suffering iNPH do not show any clinical improvement [64]. The distension of the limbic system, which is near to the lateral ventricles, could explain the cognitive and personality disorders [112]. In opposition to the latter, electromyographic and

motor evoked potential studies on patients possibly suffering iNPH, showed that motor disorders have a greater relation with extrapyramidal tracts than with pyramidal ones [117].

The hydrodynamic theory attributes the symptoms appearance to the decrease of intracranial compliance and of the brain blood flow [42] and likewise because of a CSF dynamic disorder [29]. Other studies say that it is frequent that there are changes in the periventricular white matter and the deep white matter, which also could explain the symptoms [108]. This could be related to the idea of the second hit theory [12], and as was already mentioned, it proposes that the aging and ischemia of the deep white matter could be responsible for the symptomatology present in iNPH [14] It is important to mention that this symptomatology presents great variations in

relation to the nature of the symptoms, the manner of presentation, severity and progression. Therefore, there is not a natural history of iNPH, which can be absolutely typified for its symptomatology [91]. Nevertheless, as has been said, the symptomatic triad describes it best, including in order (more frequent to less frequent): walking disorders [85], cognitive disorders and urinary incontinence. We will study them in this order.

Walking disorders

This is the most characteristic and prominent disorder related to iNPH. It is frequent to observe that the altered walking is accompanied by anomalous posture and a slowing down of all motor activities [8], [49]. In spite of the wide spectrum, it is found that at the initial phases of the disease appears a

form of instability and equilibrium disorder. The patient shows difficulty to begin a walk or to make a turn, which causes a slowing down and difficulty to climb stairs. This is followed by a gait with widened base, the steps become faster and shorter and there is a dragging of the feet, which seems as if they were glued to the floor, for this reason it is said that they are attracted by some kind of magnetism (magnetic walk). There is also a degree of anterior flexion of the trunk and spasticity, which is more evident in relation to the lower limbs, and because of this there is frequent sensation of fatigue in the legs and an increase of rigidity regarding the lower limbs. There is neither ataxia nor paresis of the members [112]. Although beginning to walk is difficult, once the movement has begun the activity becomes progressively normal. This difficulty to begin movements can also be seen

in Parkinson´s disease [103], likewise bradykinesia, tremor, posture instability, walking retropulsion and festination, mask facies, rigidity with or without Cogwheel Sign, among others [92]. However the fact that the movement improves with time shows a frontal motor disorder. Another way to differentiate iNPH from Parkinson´s disease relates to the rigidity of lower limbs, which in the first case is minor and in the second serious, additionally there is a permanent slowness of alternating movements [24]. Finally, the patient loses the ability to turn in bed, to stand up and to walk around.

Cognitive disorders and dementia

The neuropsychological deterioration of iNPH varies greatly, because it involves cognitive and behavioral capabilities. Also the symptoms and the severity of them vary for each patient,

because their beginning is insidious and they could become acute due to systemic processes, for example viral diseases. On the other hand, most patients show minor symptoms which progressively become worse, therefore it would be hasty to classify from the beginning this neuropsychological deterioration as “dementia” [106], [109]. Although the symptoms are progressive and chronic, affect primarily the memory and later the behavior and thought, making it impossible to perform the activities of everyday life, language is generally not affected [24]. It represents a secondary dementia, because the cause of the mental disorder is the mechanical effect of hydrocephalus on the limbic system, corona radiata and frontal lobe, and not a primary functional cortical disorder. This is supported by the fact that the symptoms are reversible by CSF shunting, and

because of this it is classified as potentially reversible dementia [24]. Other authors also would classify it as secondary by attributing it causes as ischemia of deep white matter [108]. This kind of dementia is called also “subcortical dementia”, which shows pathological subcortical alterations that can affect the functions of the frontal lobe, and for this reason it is also called front-subcortical dementia. The subcortical dementia (for example iNPH) is characterized by motor disorders, dysarthria, depression and apathy, while cortical dementia is characterized by aphasia, apraxia and agnosia. The motor disorders help to differentiate the subcortical dementia (v. g. gait apraxia and iNPH tremor) from the cortical dementia [6], because in the former they represent a primary symptom and in the latter they appear in late stages of the disease [95], [99]. In relation to subcortical

dementia, after the motor disorders, appear the cognitive ones, which evolve simultaneously [35]. The cognitive deterioration begins generally with a slight intellectual slowing down (decreased attention and concentration) and an insidious loss of recent memory. This is followed by a deterioration of the information processing speed, executive functions ability, visuoconstructive and visuoespatial abilities, the capability to perform complex calculations and abstract processes, it also can appear micrographia and lastly there is an accentuation of memory deterioration which goes even to falsification of memories (fabulations) [4].

Sphincter incontinence

This is the least frequent symptom and the one that often appears the latest. If it appears as first symptom, it is normally attributed to

urological or gynecological disorders, because normally it refers to old patients as well. At the beginning, its presence is thought to be caused by the dilation of the corona radiata with affectation to motor system, however, at late stages of iNPH it can be associated to neuropsychiatric deterioration and because of this, it is called frontal lobe incontinence, given the fact that it seems that the patient does not care about the incontinence [112]. Generally, its beginning is insidious and the patients describe it as an imperious need to urinate (urinary urgency) or simply as frequent micturition (pollakiuria). There can be different degrees of incontinence, which can become continuous incontinence or frontal lobe incontinence. Some studies make references to cases in which anal sphincter incontinence appear at final stages of iNPH [4].

Paraclinical diagnosis

Radiological diagnosis is a key feature in relation to iNPH. Along the years, tests like MRI and CT have become essential tools in its diagnosing and monitoring. Additionally, these tests have helped to understand the morphological changes of iNPH, to relate them to the clinical characteristics of the disease and to explain its pathophysiology. However, in recent years and due to technological progress, the radiological tests, especially MRI, have been used in very promising ways. We are speaking of functional radiology, where through quantification of images with phase-contrast [33], through the use of biological markers [107], among other techniques, it has been possible to learn the dynamic between intracranial fluids and the spaces containing them. This has provided a greater certainty in differential diagnoses and also in relation to

the prognosis regarding the patients who received a CSF shunt. As has been already said, the diagnosis of iNPH tends to be unclear. It is not easy to establish a differential clinical diagnosis between iNPH and dementia multi infarct, Alzheimer type dementia and Parkinson´s disease. Because of these, research endeavours try to establish means of characterizing them [97]. It should not be forgotten that MRI cannot be used on patients with metallic implants or who are claustrophobic, besides it is more expensive. Nevertheless MRI is preferred for the primary study and diagnosis of iNPH, and it is considered that CT is a good radiological mean for the postsurgical monitoring of patients. MRI shows a high sensitivity regarding the brain tissue, besides it provides the possibility of a better evaluation of the posterior cranial fossa and ventricular

narrowing (foramina of Monro, the median aperture and the lateral recess of the fourth ventricle), also it allows to visualize the CSF dynamic, which in iNPH patients is hyperdynamic. This hyperdynamic flow is an indicator of positive prognosis in case of a CSF shunting, but the fact that it does not exist, does not preclude the existence of iNPH [31].

The image tests (CT or MRI) should be done in order to confirm the ventricular enlargement, to rule out obstructive causes of this enlargement and also rule out brain atrophy or false hydrocephalus (ex vacuum). Besides, through these tests it can be seen the morphology of the ventricular system and brain parenchyma. Morphological changes like lateral ventricles enlargement, with a round contour of its frontal horns, a corpus callosum, which is flatten and cranially displaced against

the falx cerebri, a round third ventricle bulging toward its floor or exhibiting dilation of its anterior and posterior recesses, and a less dilated fourth ventricle are frequently associated with iNPH. There is also in iNPH a greater dilation of the temporal horns, which helps to differentiate it from brain atrophy [42], [54]. The Evans index should be quantified [32]. This index should be equal to or greater than 0,3 in iNPH cases. It reflects the increased rate of ventricular size in relation to the diameter of the cranium [91]. The presence of a periventricular edema is due, according to the hydrodynamic theory, to the fact that the greater transcortical pulsatile pressure acts on the ventricular wall and also that this pressure is stronger at the horns of the lateral ventricles, which would explain the presence of edema in these places. As was already mentioned in regard to the pathophysiological mechanisms,

this theory explains phenomena like the dilation of the lateral sulcus (Sylvian fissure), the presence of subarachnoid cysts, because they both are located near the great brain arteries, and that the fourth ventricle does not appear with a clear size increase, because its proximity to the spinal sack, which has a high compliance [42].

Treatment

To speak about the iNPH treatment is not simple [17], [67], given the fact that there are some aspects related to it which are not clear. In other words, not being clear the pathophysiological mechanism which explains it, the symptomatology that characterize it and the radiological findings that describe it, also it is not clear the natural history that defines it and much less the way to treat it [18], [50], [66]. Thus when we encounter a patient, whom

we suspect of suffering iNPH, there remain always questions without answer like: is it really iNPH? and if it is, is the patient already at the point of no return?; if he is operated, will he improve and how great will be that improvement? On the other hand, iNPH involve persons of old age with more than one comorbidity factor characteristic of their age, which could make the surgical act as such and the possible postsurgical complications even more riskier for the patient than the normal symptomatic progression of the disease [55]. The ventriculoperitoneal shunt is the most used [9]. The risk of CSF hypodrainage depends on the conditions of the abdominal cavity. Excluding this one, the most usual complications, common to all ventricular systems, are CSF hyperdrainage (cephalalgia, chronic subdural hematomas and subdural hygromas), the ones related to a foreign body

implantation (bleeding, infections, catheter obstruction and dislocation) and the ones related to a malfunction of the valve system (valvular siphonage and damage) [92]. The type of valve recommended for iNPH is a debated subject [69], [80]. However, there is some consensus in preferring the use of adjustable valves, which allow establishing low pressures. In case of siphonage, it is recommended the use of additional antigravitational and anti-siphon devices [92], [90]. The hydrodynamic theory, based on its pathophysiological proposal, offers not only the CSF shunt as a possible treatment, but also the third ventricle ventriculostomy [37], [36] and the posterior fossa decompression as surgical measures against iNPH [42]. These three surgical procedures can theoretically eliminate the cause of iNPH, in case they normalize both the hemodynamic conditions of

the nervous system and the CSF flow, which at the end restores the intracranial compliance. This is another unanswered question by the CSF bulk flow theory, given the fact that it cannot explain the reason why both the posterior fossa decompression and the ventriculostomy of the third ventricle can improve the clinical symptoms and the radiological findings, and none of these procedures intervene with the absorption of CSF at the arachnoid villi. After the CSF shunt, the brain veins that were compressed re-dilate, which increases the intracranial compliance, thus arterial pulsation decreases, the venous resistance diminishes and the brain blood flow increases. In the case of a ventriculostomy of the third ventricle, an opening on the floor of this ventricle is created surgically. This communicates the CSF flow between the ventricular system and the subarachnoid

space. This communication increases the CSF ejection from the ventricle in each cardiac systole, which decreases the intraventricular pulse pressure. This decreased intraventricular pulse pressure diminishes the transcortical pulsatile pressure, which in turn diminishes the ventricular size and secondarily allows the expansion of the cortical veins and of the subarachnoid space. As has already been seen, the expansion of the cortical veins increases the intracranial compliance, diminishes the venous resistance and restores the brain blood flow.

3 Part II - Clinical Investigation

3.1 Research Questions

This doctoral thesis in addition to summarizing and reviewing dynamic pathophysiological mechanisms that might explain iNPH - tries to

contribute to the establishment of a diagnosis and treatment protocol regarding those patients, who are suspect of suffering from iNPH. As has been said in part I, even if there are at least two components of the Hakim's triad present and the radiological findings comply with ventriculomegaly, there is at least a 30% chance of non-improvement after shunt treatment. Furthermore, if only one symptom of the triad is present, there is much less certainty regarding the clinical improvement after the CSF shunt. The placement of a CSF shunt valve implies important risks of complications however, both in the short and long run, which have the potential not only to decrease the quality of life of patients, but being life threatening. For this reason, clinical and radiological findings are supplemented - especially in cases of possible iNPH - by additional diagnostic procedures. One

approach is computerized overnight monitoring and recording of intracranial pressure (ICP), which tries to identify the disease through the interpretation of the physiological and pathophysiological ICP dynamics. The second approach is computerized ICP recording during a lumbar infusion study (volume challenge) and interpretation of the resulting ICP increase.

Therefore, this work will try to relate the role of computerized analysis of intracranial pressure and cerebrospinal fluid dynamics to the diagnosis of idiopathic normal pressure hydrocephalus and investigates the effect of a positive response after three days lumbar drainage on the intracranial pressure derived variables. Finally, the outcome result 6 months after shunt implantation will be related to the initial findings.

In keeping with the hydrodynamic theory of hydrocephalus where a low compliance is in the core of the pathophysiological framework we hypothesize that our patient cohort will show indices of decrease compliance in overnight monitoring and lumbar infusion study.

The second hypothesis is, that a three day lumbar drainage trial resulting in a clinical improvement of the patient will also result in an improvement of parameters in the sense of an improved craniospinal reserve capacity and compliance.

3.2 Methodology

This used data set comes from a retrospective analysis that covers a 30 months period (from November, 2008 to May, 2011). From all patients who were evaluated for the diagnosis of probable or possible iNPH only those

patients were selected for this thesis who fulfilled the below named inclusion criteria, received the full clinical evaluation protocol plus computerized overnight monitoring of intracranial pressure, plus a lumbar infusion test, plus three days lumbar drainage protocol. From this cohort only those are included in this thesis who were classified as possible shunt responders, received a VP shunt in consequence and had a full clinical follow-up six months postoperatively.

Sample

This highly selected patient cohort comprises 21 patients The actual number of patients seen, evaluated and if positive during tests treated for iNPH was much higher (> 100 patients). However, all others either did not meet all inclusion criteria for this analysis or had received clearly positive spinal tap tests in

outside departments or institution, identifying them as possible shunt responders. This latter group of patients was treated by VP shunt insertion right away and not subjected to the extended protocol described below.

This protocol was applied to patients with uncertain or negative result of a simple spinal tap test applied elsewhere. Furthermore it was applied as standard of care to all patients who presented initially at out institution with suspected iNPH.

Inclusion criteria

- Presenting at least two of the symptoms of the Hakim triad, one of them had to be gait disorder.
- Imaging that confirms ventriculomegaly (Evans index >0,3) and rules out any other obstructive process.

- Suspicion of iNPH, not associated to infection, hemorrhage, surgery or previous trauma.
- Absence of any sensor-motor disability (visual, auditory, etc.) that prevents the patient from fulfilling the clinical evaluation of the protocol.
- Absence of another type of dementia.
- Completion of the full clinical evaluation protocol and thereafter placement of ICP sensor, ICP monitoring for at least 24 continuous hours before the lumbar infusion test.
- Insertion of lumbar drain and lumbar infusion study.
- CSF drainage for 48 - 72 continuous hours and under simultaneous and continuous monitoring of intracranial pressure.

- Clinical evaluation immediately after removing the lumbar drainage and the intracranial ICP sensor.
- Identification of possible responder:

  A) Clinical improvement in walk test or pegboard test of $\geq$ 10% plus subjective improvement according to patient or relatives.

  B) Clinical improvement in walk test or pegboard test of 5-10% plus subjective improvement plus one of the following values of the supplemental tests: initial overnight monitoring: mean RAP >0,6, or mean AMP > 1 mmHg, or R_{out} > 13 mmHg*min^{-1} or PVI <15 ml, or E > 0,15 1/ml.
- Ventriculoperitoneal shunt system inserted between 4 to 8 weeks after evaluation.
- Clinical re-evaluation at 6 months.

Materials and Methods

This study includes two sets of diagnostic tools, which were used

1) a clinical evaluation and
2) computerized monitoring of intracranial pressure at rest, under lumbar infusion test and after lumbar drainage.

Clinical Evaluation

All patients were evaluated at the hydrocephalus outpatient clinic of the Department of Neurosurgery at the Tübingen University Hospital, where it was confirmed that they fulfilled the inclusion criteria of possible or probable iNPH. After admission to the hospital, the full clinical evaluation protocol was performed.

The protocol consists of: determination of the comorbidity index, the modified scale of Kiefer,

gait evaluation, the Pegboard Test and the Mini Mental Test. The comorbidity index was used only once, at the moment of admission. The modified scale of Kiefer was used twice (1) before the evaluation and (2) at the 6 months follow-up control after CSF shunt placement. The gait evaluation, the Pegboard Test and The Mini Mental Test were applied three times, (1) before evaluation (2) after the lumbar catheter had drain at least 500 ml of CSF in a period of no less than 48 continuous hours, and (3) at the 6 month follow-up visit after ventriculoperitoneal shunt placement.

Comorbidity index (CMI): It was determined in the initial questioning. The CMI was introduced by Kiefer [61]. It represents a tool for different pathologies and their relation with the iNPH [76]. The CMI establishes the existence of known cerebrovascular disease, disease of

heart or the peripheral vessels (including hypertension) and as a systemic risk factor diabetes mellitus. Lemcke [68] et al. reported that the comorbidity factors are a statistically significant predictor of the quality of the clinical outcome for these Patients. The greatest value is 23 points, which corresponds to a patient that has a disease associated to all areas that are covered by this index. The inquiries about these factors are made only once, they are not evaluable by physical examination and they belong to the clinical history of the patient.

Modified Scale of Kiefer [60]: (Homburg-Scale according Kiefer and Steudel) This scale allows the evaluation of all symptoms that characterize iNPH. Additionally, it considers other symptoms like headache and vertigo. These two might also be present in iNPH. The greatest value is 29 points, for patients with a

high degree of disability and dependence. The best value is 0 points, which corresponds to asymptomatic individuals. Value above 8 points in the initial evaluation is considered a good predictive response factor for patients with iNPH. Using the Kiefer Scale it is possible to calculate the NPH recovery Rate [77]. It is calculated according to the equation: [(Kiefer Initial Value – Kiefer Value 6 Mo. after VP-Shunt / Kiefer Initial Value) x 10]. The results are classified according to Black Grading Scale for Shunt Assessment [7]. An improvement ≥7 is considered as Excellent, ≥5 as Good, ≥3 as Fair, ≥ 2 as Transient and <2 as Poor. Values of the NPH Recovery Rate are expressed in Points.

Gait Evaluation (number of steps in relation to time in seconds): Gait disorders are the predominant symptom of iNPH. The test

measures the number of steps and time in seconds that are needed for the patient to walk 10 m. This is done three times in a row and then an average value is obtained. The lower the number of steps and shorter the time are, the more secure and fast the gait of the patient is interpreted to be. In our work, it is only taken into account as a control measure the time in seconds.

Grooved Pegboard Test [105]: This test belongs to the protocols of neuropsychological evaluation in psychogeriatrics. It is one of the principal tests in order to evaluate the visuo-spatial and visuoconstructive perception, besides being a test of medium level cognitive demand. It evaluates the hand skill that requires complex motor-visual coordination [4]. It is a test of handling dexterity that consists of a board with 25 holes with random oriented

excavations and the pegs are to be inserted in order from left to right and from above to below. The evaluation measures the time in seconds required to accomplish the task. Using the dominant hand, it is considered normal for patients between 50 and 59 years of age to complete the task in 68,10 seconds (SD: 9,42 seconds) and for patients older than 60 82,70 seconds (SD: 18,70 seconds).

Mini Mental Test (Mini Mental State Examination - MMSE) [105], [34], [4]: This test was used because of its brevity and simplicity in order to make a neuropsychological evaluation. Besides, it is of easy application and widely used by physicians. Despite the fact that it does not define adequately the early cognitive alterations in NPH, it has been included in this study, because it provides a fast and global measure of the cognitive

alteration´s severity and allows to quantify the patient´s degree of cortical dementia. The greatest value is 30 points and if the score is lower than 24, it indicates the presence of dementia.

Intracranial pressure monitoring

Intracranial pressure monitoring (initial, lumbar infusion test [58] and lumbar drainage) [99]: must be defined as a concept of ICP visualization, control and data recollection method. ICP was monitored continuously. These data allow to analyse and interpret 1) the time course and dynamics of the mean intracranial pressure (ICP), the ICP amplitude, the correlation index of mean intracranial pressure and pressure amplitude (RAP) which is related to the cerebrospinal reserve capacity or compliance and the magnitude of ICP slow wave (SLOW).

The lumbar infusion test is a diagnostic test, which provides data regarding Elastance (E) and Volume Pressure Index (PVI) of the intramural (intraspinal and intracranial) compartment and a measure of CSF outflow resistance (R_{out}) [102]. CSF drainage of 30-50 ml by an isolated lumbar puncture (spinal tap test) has been traditionally used to assess - besides CSF pressure - the response to shunting. However, it could be shown, that a 3 days lumbar CSF drainage protocol via a lumbar catheter has a higher predictive value regarding shunt response and is considered the gold standard [91].

In this study, an intracranial and intraparenchymal ICP sensor (Neurovent-p, Raumedic AG, Helmbrechts) was placed under local anesthesia at the Kocher´s point [40]. Later the intracranial sensor was connected to the Raumadic Datalogger MPR1

monitor to initiate the ICP recording. The MPR1 was connected via USB to a computer, were ICP data were online sampled by ICM + monitoring software (Cambridge University Enterprise, Cambridge, UK).

The ICP monitoring was performed for at least a complete night before conducting the lumbar infusion study, which took place after a lumbar drain was placed under local anesthesia.

The patient is warned about possible inconveniences during the test and that in case of strong headache or neck pain, he should notify it immediately in order to suspend the test. Then the patient was positioning supine in the bed for 15 minutes, staying calm, not speaking and not moving. Baseline ICP recording was done for 15 minutes. Thereafter an infusion of Ringer solution through the lumbar drain at a rate of 1.5 ml per minute was started. The infusion

was terminated if the ensuing ICP increase resulted into a new equilibrium with a new ICP plateau for at least 10 minutes. A premature termination was performed if the patient became symptomatic or if the intracranial pressure increased over 40 mmHg. After termination of the lumbar infusion, ICP recording continued for further 10 minutes.

Thereafter CSF was drained at a rate of 7 - 8 ml per hour for 48 to 72 hours. By this means it simulates the patient having a CSF shunt. ICP recording was contused during the nights. After confirming that 500 ml had been drained, both the intraparenchymal ICP sensor and the lumbar drain were removed under local anaesthesia.

Finally, the clinical evaluation protocol (gait evaluation, Pegboard Test and Minimental Test) was applied again.

After analyzing the clinical and monitoring results, a decision was made if the patient was considered a responder (improvement in quantitative tests by 15%) and a shunt treatment should be offered. In this case they received a VP-Shunt and were monitored using the same protocol of clinical tests 6 months after surgery. Those patients without a clinically improvement (<15%) were classified as non-responders and were informed that the chance of long-term improvement would be as low as 25% according to the results of Marmarou [73], [74] and the recommendation for a shunting procedure was weak.

The responder patient was discharged with an appointment for a CSF shunt placement in the following 4 to 8 weeks.

Values and interpretation of monitoring

The software sampled the ICP signal at a rate of 100Hz and calculated mean values per minute. On the basis of this AMP, SLOW and RAP were calculated. During infusion studies mean values were calculated every 10 s [21], [102], [115]. Values of continuous monitoring were assed only overnight during sleep from 11 pm to 6 am to minimize positional and movement artifacts and to discover nocturnal ICP dynamics in response to vasogenic pressure waves during REM phase of sleep.

Intracranial Pressure (ICP): it is the result of the circulatory dynamics between intracranial CSF, and blood. It is represented through the formula: $ICP = ICP_{CSF} + ICP_{vascular}$. Both components are dynamic and multifactorial. ICP_{CSF} could be represented as the sum of the resistance to the CSF outflow multiplied by its

formation volume and the sagittal sinus pressure [10], [86]. It is considered that the $ICP_{vascular}$ depends on factors like autoregulation, arterial pressure and blood outflow through the veins. In iNPH the ICP is normal or slightly elevated. Its value during the monitoring should be initially <15 mmHg.

Amplitude (AMP): it is the ICP pulse amplitude, normally it increases simultaneously with intracranial pressure increase [87]. It can be assessed as diastolic - systolic ICP amplitude and analyzed over time (time domain method). This way of calculation pulse by pulse is complex and prone to artifacts and was not used by our software. Here, the so called frequency domain method was used, where amplitude was calculated as the first harmonic after Fourier transformation of the ICP signal, relating to the heart beat component of the

intracranial pressure wave and called AMP [21]. When baseline AMP during sleep is elevated >1 (corresponding to a diastolic-systolic amplitude of > 3,5-4 mmHg), there is a suspicion of decrease in intracranial compliance.

RAP Index: The RAP index (correlation coefficient [R] between the pulse amplitude [A] and the mean intracranial pressure [P]) [62], is derived by linear correlation between 40 consecutive, time-averaged data points of pulse amplitude of ICP (AMP) and mean ICP, acquired within a 6 second-wide time-window. RAP describes the degree of correlation between AMP and mean ICP over short periods of time (~ 4 minutes). Theoretically, the RAP coefficient indicates the relationship between ICP and changes in intracerebral volume - the ‘pressure-volume’ curve. RAP

coefficient close to 0 indicates a lack of coupling between the changes in AMP and the mean ICP. This denotes a good pressure-volume compensatory reserve, i.e. the 'working range' is still in the horizontal part of the curve. When the pressure-volume curve starts to increase exponentially, AMP co-varies directly with ICP and consequently RAP rises to a maximum of +1. This indicates a low compensatory reserve [115], [63].

Slow intracranial pressure waves (SLOW): they are the result of changes in brain blood volume with a period of 20s to 2 min [63]. They are also called Lundberg B waves [72]. They are thought to be related to the metabolism of brain tissue, because they are associated to the fluctuation of blood brain velocity flow and arterial pressure. If there is presence of these curves in more than 80% of the monitoring

taken place when sleeping, the placement of a CSF shunt is recommended [89].

The software, using spectral analysis (Fourier transform) calculates a variable, representing the equivalent amplitude (i.e. the amplitude of a sine wave bearing the same energy) of the slow waves, ‘SLOW’ [21].

Values and interpretation of lumbar infusion study [21] [115]
CSF outflow resistance (Rcsf): is calculated as the difference between the value of the plateau pressure (during infusion) and baseline pressure, divided by the infusion rate Normal value: (>10 - <13 mmHg/(ml/min). Elevated R_{csf} (>13 mmHg/(ml/min) denotes disturbed CSF circulation typically for iNPH [11], [12].

Elastance (E): describes the rigidity of the cerebrospinal system, which is determined by the capability to displace a volume of cerebrospinal blood. It is an unspecified value, that in iNPH ranges between >0,10 and <0,15 l/ml.

Pressure volume index (PVI): it is the volume amount that has to be administered in order to duplicate the intracranial pressure average. If it is under 15 ml (<15 ml), it means that the adaptability is diminished and there is the suspicion of iNPH.

3.3 Data management and Statistical Analysis

The data of the initial clinical evaluation, the clinical evaluation after 3 days lumbar drainage and from the intracranial pressure monitoring and the lumbar infusion test were

recorded anonymously in an Excel table, designed according to that purpose. Results of the clinical evaluation at 6 months after the VP-Shunt implantation were added later.

Finally, the data from the clinical response both after the lumbar drainage and after six months of the CSF shunting were compared to the initial clinical evaluation.

In order to test the hypotheses all indicated statistical tests will be discussed in the following section. To describe the variables and their distributions, tables and graphics were used such as bar charts, histograms, pie charts and box plots.

Considering the small number of cases (21 patients) and the distributions of the variables all analyses were based on non-parametric models. Parametric methods like t-Tests and the Pearson correlation demand specific assumptions, which are not met in this study,

especially because of the number of cases as well as the assumption of normality and equal variances between samples. Therefore only non-parametric statistical tests have been used [13].

To examine the differences between the clinical tests and monitoring parameters a repeated measurements design has been used. There were different points of time when the tests were conducted and the parameters were measured, which refers to dependent samples. To test for significance when only 2 dependent groups (e.g. initial vs. After VP-Shunt) were involved, the Wilcoxon signed-rank test was used. In case of testing 3 dependent groups (e.g. initial vs. during Lumbar Infusion vs. after VP-Shunt) the Friedman-Test was the indicated statistical method. When the Friedman-Test showed a significant result, post-hoc tests in the form of

pairwise comparisons have been conducted to investigate which groups differ significantly. To avoid the cumulation of Type I error, caused by multiple testing, the p-values were adjusted using the Dunn-Bonferroni method [27]. Additionally the descriptive statistics to accompany the tests like minimum, maximum and the quartiles, were also calculated and presented in the output.

To test for the relations between variables the correlation coefficient Spearman's Rho was used. The correlation coefficient can range from-1 to +1, where 0 stands for non-related variables. A value higher than 0 (or positive) shows a positive correlation, a negative value shows a negative correlation. Values of -1 or +1 would show perfect correlation [19] suggested the following effect-sizes for a correlation:

< 0,1 no effect

0,1 - 0,3 small effect

0,3 - 0,5 medium effect

> 0,5 large effect

Therefore, the starting or (null) hypothesis (H_0), assumes that the improvement of these patients after the VP-Shunt implantation is not significant, and second, the probable or alternative hypothesis, assumes that the effect of the treatment is significant (H_1). Due to the fact that all hypotheses regarding correlations were one directional all correlations were tested one-sided. For all statistical tests a significance level (α-level) of p=0,05 was determined. If a result shows a p-value > 0,05 the test is not significant and therefore the alternative hypothesis cannot be supported and the null hypothesis has to be retained. If a result shows a p-value ≤ 0,05 it is a statistical significant result and the alternative hypothesis

can be supported while the null hypothesis will be rejected. In detail we distinguish the following levels of statistical significance:

$p > 0,05$ not significant

$p \leq 0,05$ significant

$p \leq 0,01$ very significant

$p \leq 0,001$ highly significant

All analyses were conducted using Microsoft Excel 2010 and IBM SPSS Statistics Version 22.

It is important to mention, that in the SPSS Output the p-value is always called “Sig.” which stays for significance. Furthermore a p-value of ,000 means always $p < 0,001$.

4 Results

4.1 Date. Table 1

UKT / iNPH		Clinical Evaluation Initial				Initial Monitoring			Monitoring during Lumbar Infusion Test							Monitoring after Lumbar Drainage			Clinical Eval. after Lumbar Drainage			Clinical Evaluation 6 Mo. after VP-Shunt		
Pat. Nr.	Age	Comorbidity Factors	Walk-Test / Time (Sec.)	Pegboard Test / Time Sec.	Minimentaltest / Points	Kiefer-Total / Points	ICP [mmHg]	Amp [mmHg]	Slow [mmHg]	RAP	ICP plateau [mmHg]	AMP plateau [mmHg]	Slow plateau [mmHg]	Rcsf [mmHg*min/ml]	Elastance [1/ml]	PVI [ml]	ICP [mmHg]	AMP [mmHg]	Slow [mmHg]	RAP	Walk-Test / Time (Sec.)	Pegboard Test /Time Sec.	Minimentaltest / Points	Kiefer-Total / Points	Walk-Test / Time (Sec.)	Pegboard Test / Time Sec.	Minimentaltest / Points	Clinical Improvement (Subjective)
1	72	0	7,5	77	24	4	9,41	1,63	0,813	0,847	20,07	5,16	1,8	7,35	0,35	6,65	-1,86	0,94	0,67	0,28	10,0	68	27	4	7	63	30	Improve
2	83	1	60	350	18	8	10,27	2,00	1,49	0,708	35,34	6,18	3,77	16,83	0,20	11,56	2,35	1,10	0,43	0,29	54,0	320	24	7	36	180	26	Improve
3	71	3	15	200	26	5	10,49	1,21	2,35	0,41	29,77	2,98	2,77	6,86	0,09	25,09	8,59	0,45	1,64	0,43	13,0	24	28	8	13	146	25	Little improve
4	70	3	14	162	28	3	2,72	1,43	1,04	0,838	23,74	5,96	2,62	14,00	0,39	5,90	0,46	1,49	0,35	0,44	14,0	100	27	2	12	90	29	Improve
5	73	1	9,6	163	27	4	17,40	1,90	1,67	0,831	38,30	6,97	3,55	14,10	0,76	3,04	7,84	0,93	0,72	0,22	7,0	150	29	4	10	130	24	Improve
6	84	0	60	nm	4	22	3,67	1,33	1,56	0,646	24,20	6,16	2,55	12,66	0,15	15,60	7,8	1,25	0,748	0,60	60,0	785	25	10	30	nm	20	Improve
7	76	2	12	224	5	8	6,07	1,54	2,21	0,785	37,03	7,92	7,42	18,24	0,18	12,67	7,5	1,63	0,928	0,66	9,0	180	19	11	10	178	15	Improve
8	76	0	18	160	18	13	15,62	1,94	1,46	0,879	44,29	5,7	4,3	19,22	0,45	5,11	4,64	0,801	0,763	0,51	13,0	150	22	6	16	131	27	Improve
9	75	2	9	122	28	6	9,41	1,63	0,909	0,599	20,07	5,16	1,8	7,35	0,35	6,65	1,86	0,94	0,67	0,28	8,5	130	28	4	8	129	27	Improve
10	83	5	35	500	17	9	7,01	2,26	1,52	0,85	18,67	6,62	2,24	8,12	0,12	19,53	4,07	1,57	0,831	0,645	20,0	240	20	14	70	140	9	No improve
11	80	7	50	241	23	12	2,89	1,93	1,41	0,76	8,06	4,48	2,63	7,3	0,08	28,36	9,53	1,47	1,23	0,7	44,0	270	26	17	60	280	19	No improve
12	65	0	9,2	116	25	9	0,61	1,62	1,67	0,88	25,21	7,55	3,23	16,43	1	2,31	5,3	1,25	0,92	0,8	8,0	101	27	4	18	83	29	Improve
13	73	3	13	142	24	12	0,76	1,9	0,94	0,66	24,37	6,76	2,53	15,98	0,12	19,74	2,96	1,77	1,43	0,2	6	140	26	7	13	137	23	Improve
14	59	2	9	120	26	7	3,42	1,19	0,87	0,86	21,95	4,63	2,4	12,84	0,25	9,35	2,9	0,96	0,49	0,3	9	114	27	3	7	81	30	Improve
15	81	1	11	150	19	8	7,12	3,1	1,33	0,66	18,9	5,36	4,13	8,02	1	2,31	6,01	1,87	1,61	0,65	15	235	20	7	10	121	22	Improve
16	83	5	18	155	26	13	4,91	2,09	1,83	0,45	18,36	6,09	2,48	9,54	0,1	22,65	2,1	1,91	1,48	0,1	13	240	27	12	18	125	27	Improve
17	68	2	20	177	26	14	1,56	1,38	1,36	0,545	18,64	5,23	2,34	11,39	0,09	25,19	2,88	1,21	1,25	0,451	20	149	27	7	15	185	27	Improve
18	75	6	31	142	30	15	11,38	2,65	1,34	0,78	50,36	12,7	5,42	29,4	0,11	21,47	5,79	2,06	0,75	0,7	17	125	29	14	31	156	30	No improve
19	80	1	18	292	27	8	13,62	1,33	1,9	0,62	28,7	5,61	3,23	9,62	0,29	8,04	13,6	1,2	1,6	0,3	16	200	29	8	11	130	29	Improve
20	78	3	25	270	25	8	10,49	1,21	2,81	0,71	29,77	2,98	2,77	6,86	0,09	25,09	6,63	1,1	1,92	0,48	16	210	27	6	15	230	25	Little improve
21	79	0	17	230	27	8	10,73	1,61	0,95	0,67	40,68	7,86	3,15	20,53	0,12	10,81	1,75	1,22	0,93	0,4	15	214	27	7	15	160	29	Improve
		22	200	23	9,33	7,32	1,77	1,5	0,71	27,45	6,1	3,2	12,98	0,30	13,67	4,08	1,29	1,02	0,45	18,5	197	25,76	7,71	20	144	25		

4.2 Demographic Data

Age Distribution (Years). Table 2

Age (Years)	Valid	21
	Missing	0
Mean		75,43
Median		76,00
Std. Deviation		6,501
Minimum		59
Maximum		84

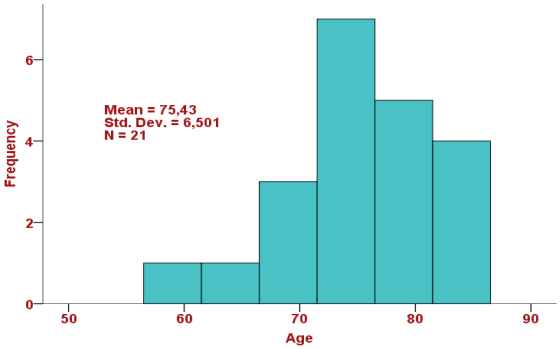


Figure 1: Demographic Data: (Age Distribution) (Years)

This figure 1 represents the demographic distribution of the sample in relation to the age. Of the 21 patients, who were parts of the study, we see that the mean age is 75,43 years and the Standard Deviation (SD) is 6,50 years. The mean and the median are very similar and they are between 70 and 80 years.

Sex Distribution. Table 3

Sex		Frequency	Percent
Valid	male	11	52,4
	female	10	47,6
	Total	21	100,0

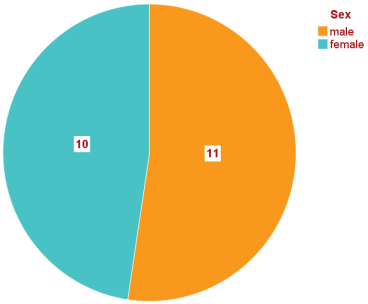


Figure 2: Demographic Data: (Sex Distribution)

This figure 2 represents the sex distribution of the sample. Of the 21 patients, who were part of the study, 11 are men and 10 are women.

4.3 Clinical Data

Clinical Evaluation (Kiefer Test / Points). Table 4

		Kiefer-Test initial	Kiefer-Test after 6 Months VP-Shunt
N	Valid	21	21
	Missing	0	0
Mean		9,33	7,71
Median		8,00	7,00
Std. Deviation		4,465	3,989
Minimum		3	2
Maximum		22	17

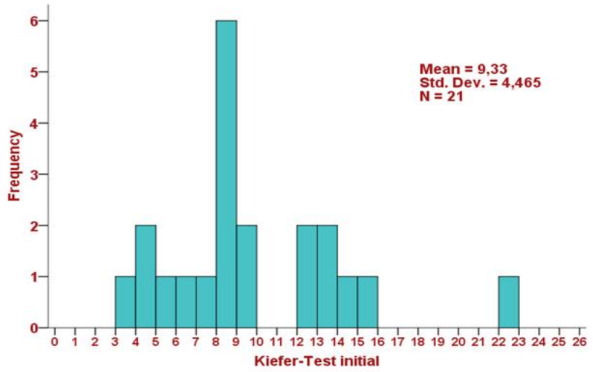


Figure 3: Clinical Evaluation (Kiefer Test Initial / Points)

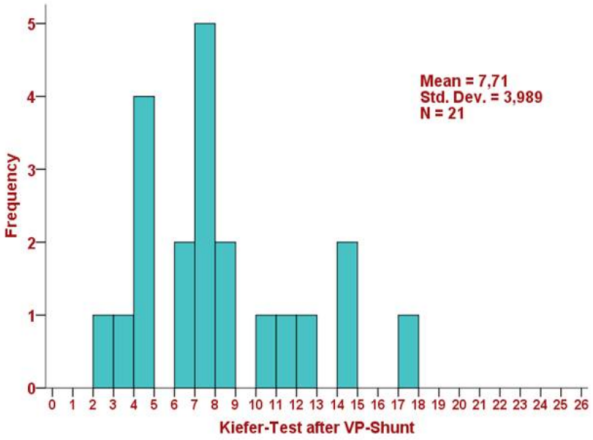


Figure 4: Clinical Evaluation (Kiefer Test after VP-Shunt / Points)

These figures 3 and 4 show the distribution of the Kiefer scale of the patients at the two moments at which it was applied during the study. A shift of distribution to the left at the six months post-operative control in relation to the initial evaluation indicates that there was a tendency to clinical improvement.

Clinical Evaluation (Walk-Test / Sec.). Table 5

Walk Test / Sec.		Walk-Test initial	Walk-Test after Lumbar Drainage	Walk-Test after VP-Shunt
N	Valid	21	21	21
	Missing	0	0	0
Mean		21,967	18,452	20,238
Median		17,000	14,000	15,000
Std. Deviation		16,2617	15,0648	16,8817
Minimum		7,5	6,0	7,0
Maximum		60,0	60,0	70,0

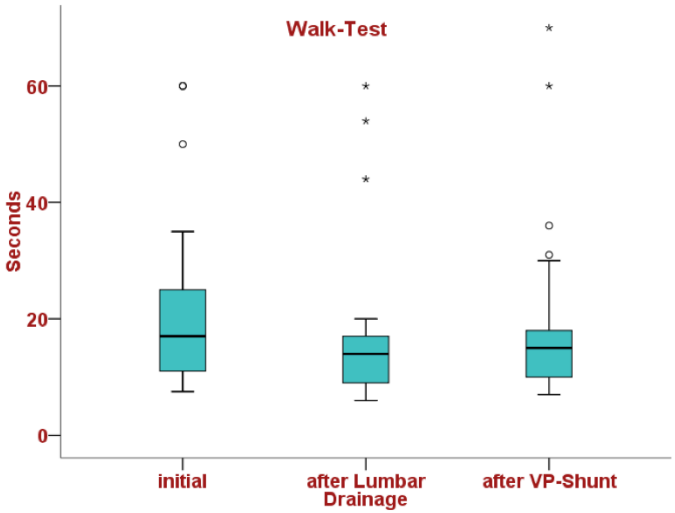


Figure 5: Clinical Evaluation (Walk Test / Sec.)

The figure 5 shows the distribution regarding the Walk Test of clinical evaluation during the three moments of the study when it was applied. In this test there was clinical improvement both after the lumbar drainage and after the six months period following the VP-Shunt implantation. There was greater improvement after the lumbar drainage. It

should be noticed that the box-and-whisker diagrams divide the distribution in four parts of 25% each. The plot as such keeps the 50% of data at the center, which is divided by a line that is the median. The figure 5 registers the extreme values of distribution marking with a little ball the patients that have results that are notoriously far of the rest.

Clinical Evaluation (Pegboard-Test / Sec.).

Table 6

Pegboard Test / Sec.		Pegboard-Test initial	Pegboard-Test after Lumbar Drainage	Pegboard-Test after VP-Shunt
N	Valid	21	21	21
	Missing	0	0	0
Mean		218,71	197,38	165,48
Median		163,00	150,00	137,00
Std. Deviation		128,944	152,287	111,263
Minimum		77	24	63
Maximum		600	785	600

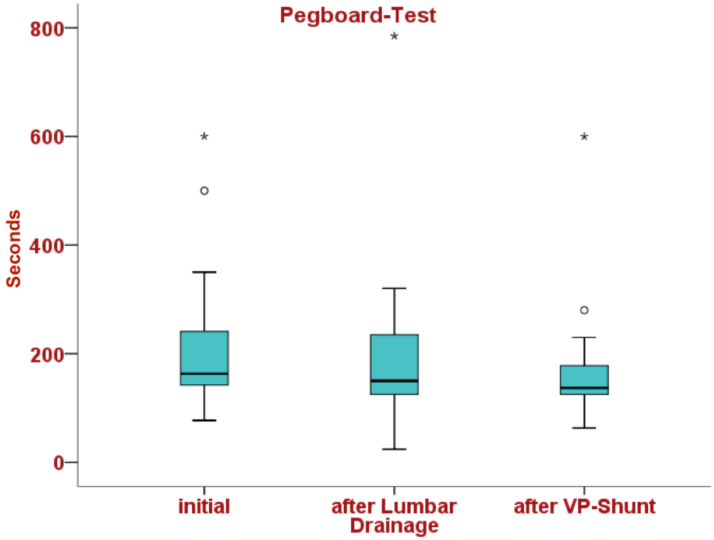


Figure 6: Clinical Evaluation (Pegboard Test / Sec.)

The figure 6 shows the distribution regarding the Pegboard Test of clinical evaluation during the three moments of the study when it was applied. In this test there was clinical improvement both after the lumbar drainage and the greatest improvement is seen at the six months control after the VP-Shunt implantation.

Clinical Evaluation (Minimental Test / Points.).

Table 7

Minimental Test / Points		Minimental-Test initial	Minimental-Test after Lumbar Drainage	Minimental-Test after VP-Shunt
N	Valid	21	21	21
	Missing	0	0	0
Mean		22,52	25,76	24,86
Median		25,00	27,00	27,00
Std. Deviation		6,983	3,032	5,416
Minimum		4	19	9
Maximum		30	29	30

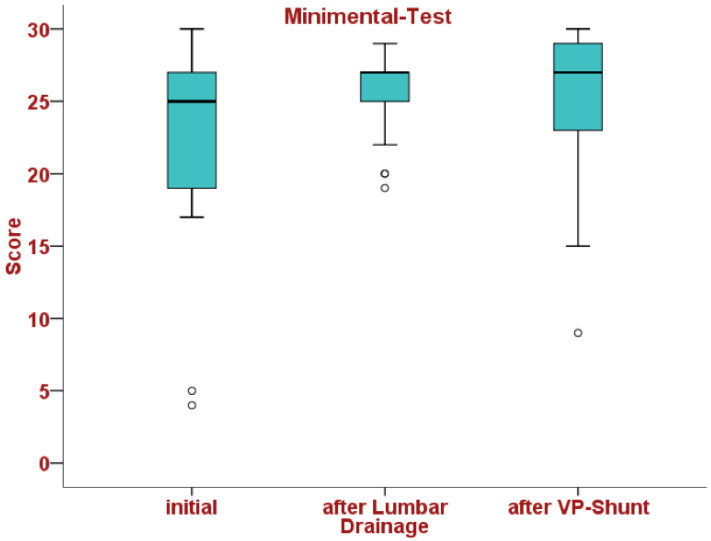


Figure 7: Clinical Evaluation (Minimental Test / Points)

The figure 7 shows the distribution regarding the Minimental Test of clinical evaluation during the three moments of the study when it was applied. In this test there was clinical improvement both after the lumbar drainage and after the six months period following the VP-Shunt implantation. It should be noticed that there was greater improvement after the lumbar drainage.

Comorbidity Factors. Table 8.

Comorbidity Factors

Comorbidity Factors	Valid	21
	Missing	0
Mean		2,00
Median		2,00
Std. Deviation		2,025
Minimum		0
Maximum		7

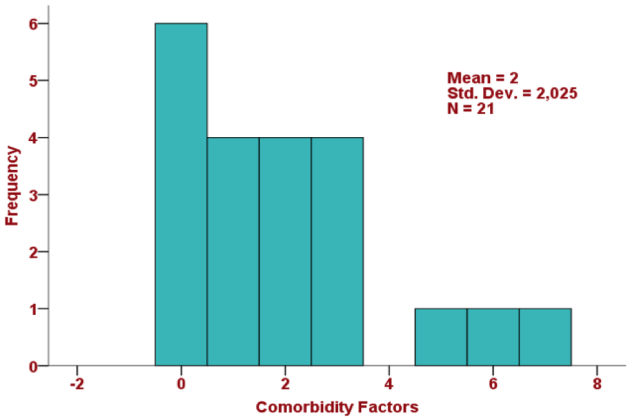


Figure 8: Clinical Evaluation (Comorbidity Factors)

This figure 8 shows distribution of comorbidity factors that the clinical history of each patient presents. The mean and the median are the same for this sample.

4.4 Intracranial Monitoring Data

Intracranial Overnight Monitoring (ICP / mmHg). Table 9

		ICP initial in mmHg	ICP after Lumbar Drainage in mmHg
N	Valid	21	21
	Missing	0	0
Mean		9,2086	4,0819
Median		8,9800	4,0700
Std. Deviation		4,80032	3,99988
Minimum		,34	-2,10
Maximum		19,96	13,60

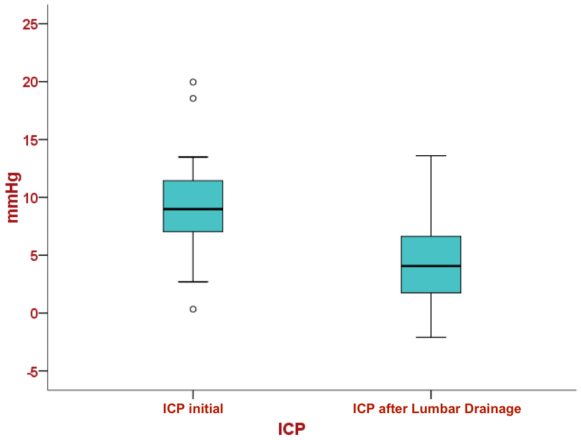


Figure 9: Intracranial Monitoring (ICP / mmHg)

The figure 9 shows the behaviour of ICP during the study. As it was described when the variables are defined, it is expected for iNPH that baseline ICP be <15 mmHg. After the lumbar drainage the ICP was lower. The figure

9 shows the variation of the ICP values in the sample after the lumbar drainage in relation to the initial monitoring. It should be noticed that after the lumbar drainage in some patients the values decreased by up to almost 12 mmHg.

Intracranial Overnight Monitoring (Slow / mmHg). Table 10

		Slow initial in mmHg	Slow after Lumbar Drainage in mmHg
N	Valid	21	21
	Missing	0	0
Mean		1,4968	1,0171
Median		1,4600	,9200
Std. Deviation		,51976	,44964
Minimum		,81	,35
Maximum		2,81	1,92

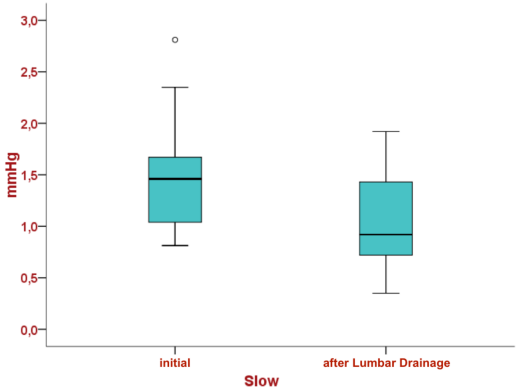


Figure 10: Intracranial Monitoring (Slow / mmHg)

The figure 10 compares the distribution value of the B waves amplitude (SLOW). The value of the amplitude is considered pathological when the mean is >10 mmHg and it is interpreted as a bad prognosis value for iNPH if the amplitude value during the infusion test is >1,5 mmHg. It should be noticed that the waves during the initial monitoring are above this threshold and close to it after the lumbar drainage. The figure 10 shows the value variation of the B waves amplitude after the lumbar drainage in relation to the initial monitoring.

Intracranial Overnight Monitoring (Amplitude / mmHg). Table 11

		Amp initial in mmHg	Amp after Lumbar Drainage in mmHg
N	Valid	21	21
	Missing	0	0
Mean		2,1210	1,2915
Median		2,0200	1,2200
Std. Deviation		,68137	,40826
Minimum		1,17	,45
Maximum		4,13	2,06

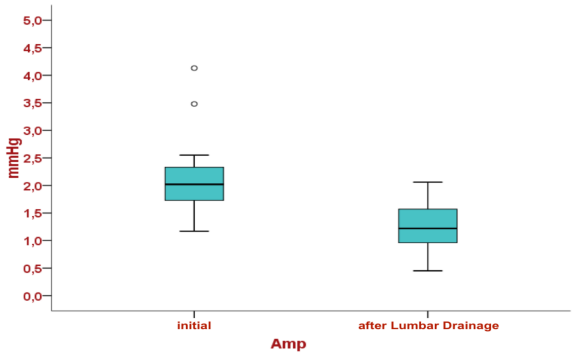


Figure 11: Intracranial Monitoring (Amp / mmHg)

This figure 11 shows through the distribution values and in a comparative way the behaviour of the AMP during the two moments of ICP monitoring. The mean of the initial AMP and after the lumbar drainage is (>1 and <2). In the variation of the AMP values for each monitoring phase (initial monitoring and after the lumbar drainage), it should be noticed that the proportionality in the behaviour of the values tends to be similar to the value variation of ICP. These both values (ICP and AMP) are very influential during this study.

Intracranial Overnight Monitoring (RAP Index).

Table 12

RAP Index		RAP initial	RAP after Lumbar Drainage
N	Valid	21	21
	Missing	0	0
Mean		,7137	,4493
Median		,7100	,4400
Std. Deviation		,13748	,19569
Minimum		,41	,10
Maximum		,88	,80

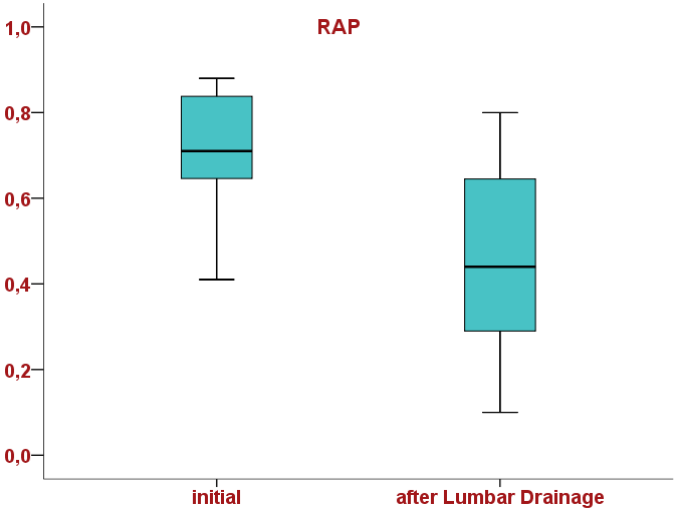


Figure 12: Intracranial Monitoring (RAP)

The figure 12 compares the distribution of the values of the RAP Index during the two evaluated moments at the monitoring. The RAP Index is the correlation coefficient between change of ICP and change of AMP. It should be noticed that the mean value during the initial monitoring (deep sleep phase) is >0,6 which reveals a lower compensatory capacity of the system. After the lumbar drainage the mean value is <0,6. It should be noticed that only four patients had initial values <0,6 and none <0,4.

Intracranial Monitoring during Lumbar Infusion study (R_{CSF} mmHg*min/ml). Table 13

Rcsf during Lumbar Infusion in mmHg*min/ml

Rcsf /mmHg*min/ml	Valid	21
	Missing	0
Mean		12,9829
Median		12,6600
Std. Deviation		5,81293
Minimum		6,86
Maximum		29,40

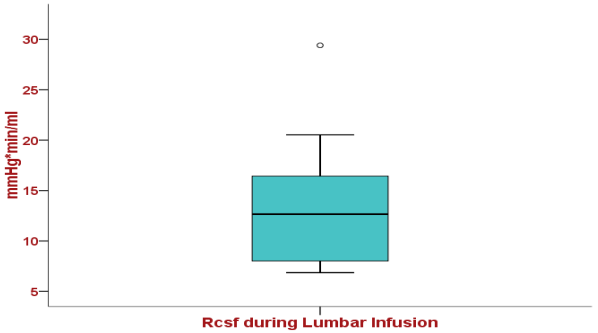


Figure 13: R_{CSF} calculated from lumbar infusion study)

This figure 13 shows the total distribution of the values of the R_{CSF} at the lumbar infusion study. Normal values are below 10 - 13, values >13 - <18 (mmHg/ml/min) are considered to represent moderate pathological elevation associated with a higher likelihood of clinical improvement after CSF diversion. Values > 18 mmHG/ml/min are considered to be severely pathologic, associated with the highest likelihood of improvement.

Intracranial Monitoring during Lumbar Infusion study (Distribution in groups of R_{CSF} in mmHg*min/ml). Table 14

Class Rcsf during Lumbar Infusion

Class Rcsf		Frequency	Percent
Valid	< 13 mmHg*min/ml	12	57,1
	13-18 mmHg*min/ml	5	23,8
	> 18 mmHg*min/ml	4	19,0
	Total	21	100,0

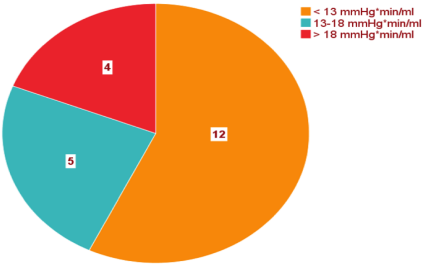


Figure 14: RCSF distribution in three groups

The figure 14 shows the number of patients that presented values lower than 13 mmHg/ml/min (12 Patients) and greater than 18 mmHg/ml/min (4 patients). Values below 13 are considered normal, above 13 elevated and above 18 highly pathological.

Intracranial Monitoring during Lumbar Infusion Study (Elastance in 1/ml). Table 15

Elastance during Lumbar Infusion in 1/ml

Elastance 1/ml	Valid	21
	Missing	0
Mean		,2995
Median		,1800
Std. Deviation		,28554
Minimum		,08
Maximum		1,00

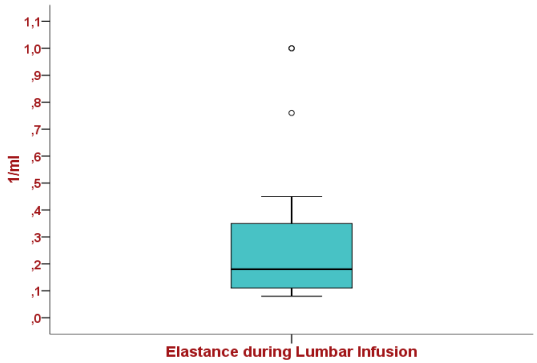


Figure 15: Elastance (calculated from Lumbar Infusion Study)

This figure 15 shows the total distribution of Elastance values calculated by lumbar infusion test. The mean is 0,30 1/ml and 11 patients

are under 0,20 1/ml. Values below 0.1 1/ml are considered normal and above 0.15 1/ml are thought to represent significant compromise of compliance and cerebrospinal reserve capacity.

Intracranial Monitoring during Lumbar Infusion Study (Distribution in groups of Elastance in 1/ml). Table 16

Class Elastance during Lumbar Infusion

Class Elastance		Frequency	Percent
Valid	< 0,10 1/ml	4	19,0
	0,10-0,15 1/ml	6	28,6
	> 0,15 1/ml	11	52,4
	Total	21	100,0

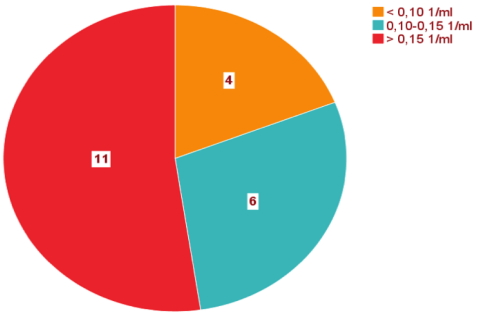


Figure 16: Elastance distribution in three groups

This figure 16 shows a classification of the distribution of Elastance calculated by lumbar infusion test. 4 Patients have values below 0.1 1/ml (considered normal); 11 Patients have values above 0.15 1/ml (considered pathological and represent significant compromise of compliance and cerebrospinal reserve capacity).

Intracranial Monitoring during Lumbar Infusion Study (PVI in ml). Table 17

PVI during Lumbar Infusion in ml

PVI / ml	Valid	21
	Missing	0
Mean		13,6724
Median		11,5600
Std. Deviation		8,64009
Minimum		2,31
Maximum		28,36

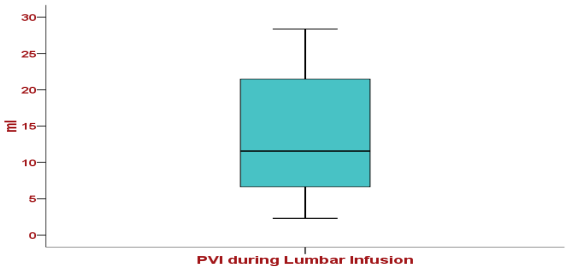


Figure 17: Intracranial Monitoring during Lumbar Infusion Study: PVI distribution

The figure 17 shows the total distribution of the PVI values (ml) in this sample during the lumbar infusion study. The mean is 13,75. 12 Patients have a PVI < 15 ml and 9 Patients > 15 ml.

Intracranial Monitoring during Lumbar Infusion Study (Distribution in groups of PVI in ml). Table 18

Class PVI during Lumbar Infusion

Class PVI		Frequency	Percent
Valid	< 15 ml	12	57,1
	>= 15 ml	9	42,9
	Total	21	100,0

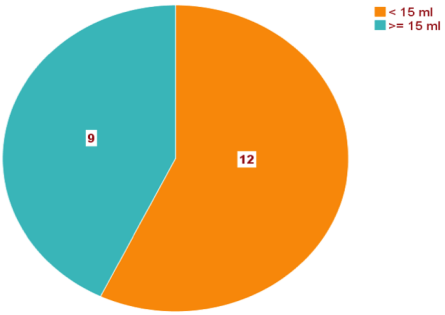


Figure 18: PVI (distribution into two groups)

The figure 18 shows the PVI values in ml regarding the studied sample. As it was already said, the pressure-volume index (PVI) is the quantity of volume that has to be administered in order to double the mean of ICP. If this index is lower than 15 ml, it is interpreted as a diminished compliance. The latter is considered as a predictive value regarding the clinical improvement after VP-Shunt implantation. The sample shows that 57% of the patients (12) presented values <15 ml during the infusion test.

4.5 Additional Descriptive Statistics

Improvement Index (Clinical Evaluation 6 months after shunt implantation). Table 19

	Poor		Fair		Good		Excellent	
	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Improvement Walk-Test	7	33,3%	2	9,5%	5	23,8%	7	33,3%
Improvement Pegboard-Test	6	28,6%	0	0,0%	1	4,8%	14	66,7%
Improvement Minimental-Test	11	52,4%	2	9,5%	0	0,0%	8	38,1%

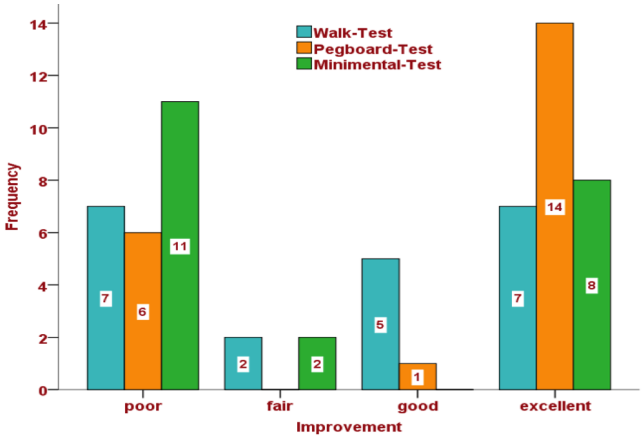


Figure 19: Improvement Index (Clinical Evaluation)

The figure 19 shows the Improvement Index in (%) regarding the three tests (Walk-Test / Pegboard Test / Minimental Test) at the six

months post-operative control in relation to the initial evaluation. The improvement index was calculated according to the equation: [(Test-Initial Value – Test-Value 6 Mo. after VP-Shunt / Test-Initial Value) x 10]. An improvement >15% was considered as Excellent, between 10-15% as Good, between 5-10% as Fair and <5% as Poor. This last value includes all cases of clinical deterioration. The test with the greatest number of patients showing an improvement index >15% is the Pegboard Test with a total of 14/21 patients. The test with the greatest number of patients that showed no improvement (improvement index <5%) was the Minimental test with a total of 11/21 patients. Regarding the Walk-Test half of the patients (11/21) showed an improvement index >15%.

NPH Recovery Rate – Improvement (Clinical Evaluation) [77]. Table 20

	Improvement NPH Recovery Rate					
	Poor	Transient	Fair	Good	Excellent	Total
Count	12	1	3	5	0	21
Row N %	57,1%	4,8%	14,3%	23,8%	0,0%	100,0%

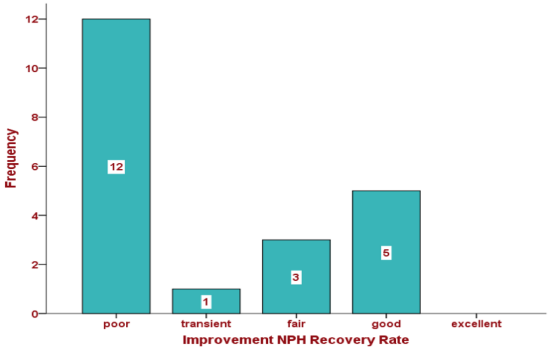


Figure 20: NPH Recovery Rate - Improvement (Clinical Evaluation)

The figure 20 shows the NPH recovery Rate. They are calculated according to the equation: [(Kiefer Initial Value – Kiefer Value 6 Mo. after VP-Shunt / Kiefer Initial Value) x 10].

According to the *Black Grading Scale for Shunt Assessment* [7] (based on the clinical grading for NPH by Kiefer) in relation with the NPH Recovery Rate an improvement ≥7,5 is considered as Excellent, ≥5 as Good, ≥3 as Fair, ≥ 2 as Transient and <2 as Poor. The long term responses after the Shunt implantation shows that 12 patients scored as Poor (57%), 4 as Fair (19%), and 5 as Good (24%) in relation to the initial evaluaiton. There was no patient with a score ≥7,5, i. e., with an Excellent long term response.

NPH Recovery Rate – Percentile Ranking (Clinical Evaluation). Table 21

NPH Recovery Rate

N	Valid	21
	Missing	0
Mean		1,2455
Median		1,2500
Std. Deviation		3,63683
Minimum		-6,00
Maximum		5,71
Percentiles	25	,0000
	50	1,2500
	75	4,5833

NPH Recovery Rate – Responder / Dichotomization. Table 22

Responder (NPH Recovery Rate)

		Frequency	Percent
Valid	Responder (>2)	9	42,9
	Non Responder (≤2)	12	57,1
	Total	21	100,0

After the NPH Recovery Rate dichotomization for Responder (>2) and Non Responder (≤2) this Table shows that the 57,1 % (12 Patients) had not responded according to this mode of outcome assessment.

4.6. Inferential Statistical – Correlation (Hypothesis)

(H1): There are differences in test-results (clinical evaluation and intracranial monitoring) between initial, after lumbar drainage and after 6 months VP Shunt implantation when the patients responding to three days lumbar

drainage trial and show indices of lowered intracranial compliance and shunting primarily these patients leads to an increase in intracranial compliance and restoration for reserve capacity by removing CSF.

(H0): There are no differences in Test-Results (Clinical Evaluation and Intracranial Monitoring) between initial, after lumbar drainage and after 6 months VP Shunt implantation in these patients.

Correlation (NPH Recovery Rate and Clinical Evaluation). Table 23

Correlations			NPH Recovery Rate
Spearman's rho	NPH Recovery Rate	Correlation Coefficient	1,000
		Sig. (1-tailed)	.
		N	21
	Improve Index Walk-Test in %	Correlation Coefficient	,298
		Sig. (1-tailed)	,095
		N	21
	Improve Index Pegboard-Test in %	Correlation Coefficient	-,154
		Sig. (1-tailed)	,252
		N	21
	Improve Index Minimental-Test in %	Correlation Coefficient	-,410
		Sig. (1-tailed)	,032
		N	21

This table shows correlation (according Spearman´s rho correlation) of differences of Test-results (Improvement Index of Walk Test, Pegboard Test and Minimental Test) after VP Shunt Implantation with NPH Recovery Rate. The Walk Test show a Significance: 0,095 and the Pegboard Test a Significance: 0,252. There is not a significant statistical correlation, this difference was no significant (p>0,05) and (H1) was rejected. About Minimental Test the significance is 0,032, this difference was significant (p≤0,05) and is accepted the (H1).

Correlation (Comorbitity Factors and clinical evaluation). Table 24

Correlations			Comorbidity Factors
Spearman's rho	Comorbidity Factors	Correlation Coefficient	1,000
		Sig. (1-tailed)	.
		N	21
	NPH Recovery Rate	Correlation Coefficient	-,202
		Sig. (1-tailed)	,190
		N	21
	Improve Index Walk-Test in %	Correlation Coefficient	-,035
		Sig. (1-tailed)	,440
		N	21
	Improve Index Pegboard-Test in %	Correlation Coefficient	-,383
		Sig. (1-tailed)	,043
		N	21
	Improve Index Minimental-Test in %	Correlation Coefficient	,508
		Sig. (1-tailed)	,009
		N	21

This table shows correlation (according Spearman´s rho correlation) of differences of Test-results (Improvement Index: Walk Test, Pegboard Test and Minimental Test) and (NPH Recovery Rate) after six months of the Shunt implantation in relation to the Comorbidity factors (CMI). The correlation between CMI and NPH Recovery Rate and Walk Test have a Significance (p>0,05) and this difference was no significant, the (H1) was rejected. The correlation between CMI and Pegboard Test and Minimental Test have a

Significance (p≤0,01), the difference was very significant, the (H1) is accepted.

Differences of Intracranial Monitoring Data (whole Sample) (Initial - after Lumbar Drainage). Table 25

		ICP Difference initial - after Lumbar Drainage	Slow Difference initial - after Lumbar Drainage	Amp Difference initial - after Lumbar Drainage	RAP Difference initial - after Lumbar Drainage
N	Valid	21	21	21	21
	Missing	0	0	0	0
Mean		5,1267	,4796	,8295	,2644
Median		5,3300	,5900	,7900	,2700
Std. Deviation		4,50512	,44382	,66870	,19486
Minimum		-2,26	-,49	-,43	-,02
Maximum		15,32	1,28	2,50	,61

Differences: Intracranial Monitoring Data (Patients) (Initial - after Lumbar Drainage / after Lumbar Infusion Test). Table 26.

These tables show the intracranial monitoring data for each patient (table 25) and differences

of the complete sample (table 26) regarding ICP, Slow, AMP and RAP at the three time points of the study. We calculated the difference between the initial night of monitoring in relation to the last night under lumbar drainage.

Table 26.

Monitoring	ID																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
ICP initial	9,37	8,06	7,66	7,99	13,49	8,27	11,44	19,96	11,68	7,04	,34	3,04	9,63	10,56	11,34	4,24	2,70	13,21	18,55	8,98	5,83
ICP during Lumbar Infusion	20,07	35,34	29,77	23,74	38,30	24,20	37,03	44,29	20,07	18,67	8,06	25,21	24,37	21,95	18,90	18,36	18,64	50,36	28,70	29,77	40,68
ICP after Lumbar Drainage	-1,86	2,35	8,59	,46	7,84	7,80	7,50	4,64	-1,86	4,07	-,53	5,30	3,96	2,90	6,01	-2,10	2,88	5,79	13,60	6,63	1,75
ICP Difference initial - after Lumbar Drainage	11,23	5,71	-,93	7,53	5,65	,47	3,94	15,32	13,54	2,97	,87	-2,26	5,67	7,66	5,33	6,34	-,18	7,42	4,95	2,35	4,08
Slow initial	,81	1,49	2,35	1,04	1,67	1,56	2,21	1,46	,91	1,52	1,41	1,67	,94	,87	1,33	1,83	1,36	1,34	1,90	2,81	,95
Slow during Lumbar Infusion	1,80	3,77	2,77	2,62	3,55	2,55	7,42	4,30	1,80	2,24	2,63	3,23	2,53	2,40	4,13	2,48	2,34	5,42	3,23	2,77	3,15
Slow after Lumbar Drainage	,67	,43	1,64	,35	,72	,75	,93	,76	,67	,83	1,23	,92	1,43	,49	1,61	1,48	1,25	,75	1,60	1,92	,93
Slow Difference initial - after Lumbar Drainage	,14	1,06	,71	,69	,95	,81	1,28	,70	,24	,69	,18	,75	-,49	,38	-,28	,35	,11	,59	,30	,89	,02
Amp initial	1,73	2,02	2,50	2,55	2,03	1,52	4,13	2,21	1,83	2,35	1,99	2,33	1,34	1,42	1,99	2,16	1,98	3,48	1,59	1,17	2,22
Amp during Lumbar Infusion	5,16	6,18	2,98	5,96	6,97	6,16	7,92	5,70	5,16	6,62	4,48	7,55	6,76	4,63	5,36	6,09	5,23	12,70	5,61	2,98	7,86
Amp after Lumbar Drainage	,94	1,10	,45	1,49	,93	1,25	1,63	,80	,94	1,57	1,47	1,25	1,77	,96	1,87	1,91	1,21	2,06	1,20	1,10	1,22
Amp Difference initial - after Lumbar Drainage	,79	,92	2,05	1,06	1,10	,27	2,50	1,41	,89	,78	,52	1,08	-,43	,46	,12	,25	,77	1,42	,39	,07	1,00
RAP initial	,85	,71	,41	,84	,83	,65	,79	,88	,60	,85	,76	,88	,66	,86	,66	,45	,55	,78	,62	,71	,67
RAP after Lumbar Drainage	,28	,29	,43	,44	,22	,60	,66	,51	,28	,65	,70	,80	,20	,30	,65	,10	,45	,70	,30	,48	,40
RAP Difference initial - after Lumbar Drainage	,57	,42	-,02	,40	,61	,05	,13	,37	,32	,20	,06	,08	,46	,56	,01	,35	,09	,08	,32	,23	,27

Correlation (NPH Recovery Rate and changes after lumbar drainage in overnight monitoring). Table 27

Correlations			NPH Recovery Rate
Spearman's rho	NPH Recovery Rate	Correlation Coefficient	1,000
		Sig. (1-tailed)	.
		N	21
	ICP Difference initial - after Lumbar Drainage	Correlation Coefficient	,170
		Sig. (1-tailed)	,231
		N	21
	Slow Difference initial - after Lumbar Drainage	Correlation Coefficient	-,066
		Sig. (1-tailed)	,387
		N	21
	Amp Difference initial - after Lumbar Drainage	Correlation Coefficient	-,259
		Sig. (1-tailed)	,129
		N	21
	RAP Difference initial - after Lumbar Drainage	Correlation Coefficient	,155
		Sig. (1-tailed)	,251
		N	21

This table 27 shows correlation (according Spearman´s rho correlation) of NPH Recovery Rate in relation to the differences of Intracranial Monitoring results after lumbar drainage (ICP, Slow and AMP, RAP). The correlation between NPH Recovery Rate and all ICM parameters (ICP, Slow, AMP and RAP)

have a significance (p>0,05). This difference was no significant and the (H1) was rejected.

Walk Test - Percentile Ranking (Clinical Evaluation). Table 28

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Walk-Test initial	21	21,967	16,2617	7,5	60,0	10,300	17,000	28,00
Walk-Test after Lumbar Drainage	21	18,452	15,0648	6,0	60,0	9,000	14,000	18,50
Walk-Test after VP-Shunt	21	20,238	16,8817	7,0	70,0	10,000	15,000	24,00

Walk Test - Friedman Test. Table 29

Friedman Test / Ranks	Mean Rank
Walk-Test initial	2,55
Walk-Test after Lumbar Drainage	1,71
Walk-Test after VP-Shunt	1,74

Walk Test – Significance (Chi-Square). Table 30

Test Statistics. N	21
Chi-Square	10,587
df	2
Asymp. Sig.	,005

Walk Test Outcome – Pairwise Comparisons.

Table 31

Pairwise Comparisons (Sample 1-Sample 2)	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
Walk-Test after Lumbar Drainage-Walk-Test after VP-Shunt	-,024	,309	-,077	,939	1,000
Walk-Test after Lumbar Drainage-Walk-Test initial	,833	,309	2,700	,007	,021
Walk-Test after VP-Shunt-Walk-Test initial	,810	,309	2,623	,009	,026

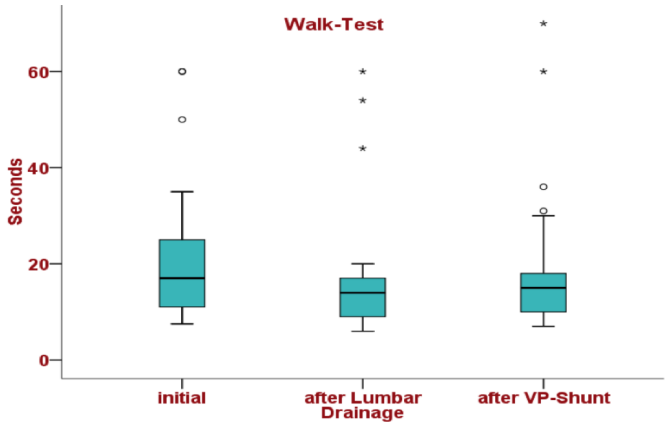


Figure 25: Walk Test Outcome (Clinical Evaluation)

These tables (28, 29, 30, 31) and the figure 25 show the outcome regarding the significance

of the Walk Test at the three time points when this test was applied (Initial, after Lumbar Drainage and after VP-Shunt Implantation). The significance of these three time points together (Chi Square) was $p<0,05$, i. e. the difference was significant and the (H1) was accepted. In the relation between the three moments separated (Pairwise comparisons) the significance was $p\geq0,05$ for the first relation (after Lumbar Drainage – after VP-Shunt), i. e. the difference was not significant and (H1) was rejected. The others two relations (after Lumbar Drainage – Test Initial, and after VP Shunt – Test Initial) show a significance of $p<0,05$, i. e. the difference was significant and (H1) was accepted. The Figure 25 shows the distribution in the outcome for the Walk Test. The best outcome is found after Lumbar Drainage.

Pegboard Test - Percentile Ranking (Clinical Evaluation). Table 32

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Pegboard-Test initial	21	218,71	128,944	77	600	142,00	163,00	255,50
Pegboard-Test after Lumbar Drainage	21	197,38	152,287	24	785	119,50	150,00	237,50
Pegboard-Test after VP-Shunt	21	165,48	111,263	63	600	123,00	137,00	179,00

Pegboard Test - Friedman Test. Table 33

Friedman Test / Ranks	Mean Rank
Pegboard-Test initial	2,55
Pegboard-Test after Lumbar Drainage	2,00
Pegboard-Test after VP-Shunt	1,45

Pegboard Test – Significance (Chi Square). Table 34

Test Statistics.	
N	21
Chi-Square	12,747
df	2
Asymp. Sig.	,002

Pegboard Test Outcome – Pairwise Comparisons. Table 35

Parwise Comparisosns (Sample 1-Sample 2)	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
Pegboard-Test after VP-Shunt-Pegboard-Test after Lumbar Drainage	,548	,309	1,774	,076	,228
Pegboard-Test after VP-Shunt-Pegboard-Test initial	1,095	,309	3,549	,000	,001
Pegboard-Test after Lumbar Drainage-Pegboard-Test initial	,548	,309	1,774	,076	,228

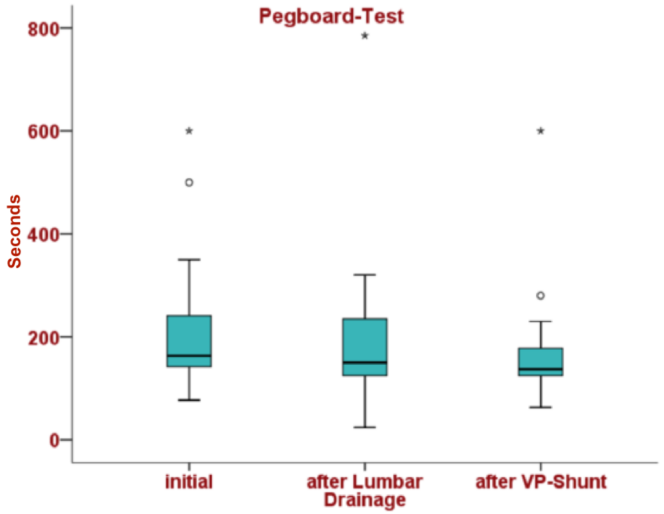


Figure 26: Pegboard Test Outcome (Clinical Evaluation)

These tables (32, 33, 34, 35) and figure the 26 show the outcome regarding the significance of the Pegboard Test at the three time points

when this test was applied (Test Initial, after Lumbar Drainage and after VP-Shunt Implantation). The significance of these three time points together (Chi Square) was $p<0,05$, i. e. the difference was significant and the (H1) was accepted. In the relation between the three moments separated (Pairwise comparisons) the significance was $p\geq0,05$ for the relations (after VP-Shunt – after Lumbar Drainage, and after Lumbar Drainage – Test Initial), i. e. the difference was not significant and (H1) was rejected. The relation (after VP Shunt – Test Initial) show a highly significance of $p<0,001$, i. e. the difference was significant and (H1) was accepted. Figure 26 shows the distribution in the outcome for the Pegboard Test. The best outcome is found after VP Shunt.

Minimental Test - Percentile Ranking (Clinical Evaluation). Table 36

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Minimental-Test initial	21	22,52	6,983	4	30	18,50	25,00	27,00
Minimental-Test after Lumbar Drainage	21	25,76	3,032	19	29	24,50	27,00	27,50
Minimental-Test after VP-Shunt	21	24,86	5,416	9	30	22,50	27,00	29,00

Minimental Test – Friedman Test. Table 37

Friedman Test / Ranks	Mean Rank
Minimental-Test initial	1,48
Minimental-Test after Lumbar Drainage	2,36
Minimental-Test after VP-Shunt	2,17

Minimental Test – Significance (Chi Square). Table 38

Test Statistics.	
N	21
Chi-Square	9,844
df	2
Asymp. Sig.	,007

Minimental Test Outcome – Pairwise Comparisons. Table 39

Pairwise Comparisons (Sample 1-Sample 2)	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
Minimental-Test initial-Minimental-Test after VP-Shunt	-,690	,309	-2,237	,025	,076
Minimental-Test initial-Minimental-Test after Lumbar Drainage	-,881	,309	-2,855	,004	,013
Minimental-Test after VP-Shunt-Minimental-Test after Lumbar Drainage	,190	,309	,617	,537	1,000

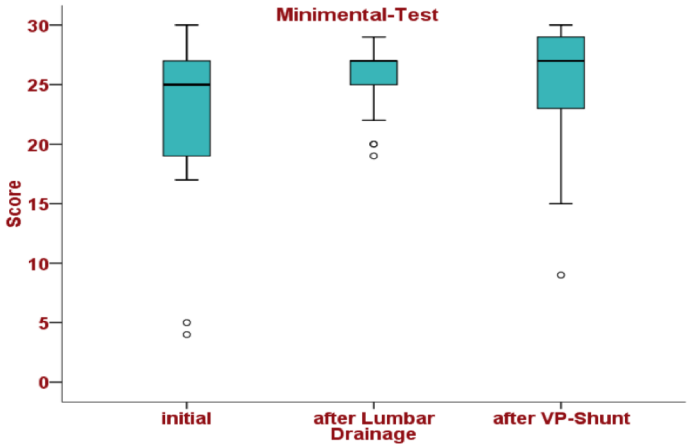


Figure 27: Minimental Test Outcome (Clinical Evaluation)

These tables (36, 37, 38, 39) and the figure 27 show the outcome regarding the significance of the Minimental Test at the three moments when this test was applied (Test Initial, after

Lumbar Drainage and after VP-Shunt Implantation). The significance of these three time points together (Chi Square) was $p<0,05$, i. e. the difference was significant and the (H1) was accepted. In the (pairwise comparisons) the significance was $p\geq0,05$ for the comparison (after VP Shunt – after Lumbar Drainage), i. e. the difference was not significant and (H1) was rejected. The other two companions (Test Initial – after Lumbar Drainage, and Test Initial - after VP Shunt) show a significance of $p<0,05$, i. e. the difference was significant and (H1) was accepted. The figure 27 shows the distribution in the outcome for the Minimental Test. The best outcome is found after Lumbar Drainage.

Intracranial Pressure (ICP) - Percentile Ranking (ICM). Table 40

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
ICP initial	21	9,2086	4,80032	,34	19,96	6,4350	8,9800	11,5600
ICP during Lumbar Infusion	21	27,4514	10,32468	8,06	50,36	19,4850	24,3700	36,1850
ICP after Lumbar Drainage	21	4,0819	3,99988	-2,10	13,60	1,1050	4,0700	7,0650

ICP – Friedman Test. Table 41

Friedman Test / Ranks	Mean Rank
ICP initial	1,86
ICP during Lumbar Infusion	3,00
ICP after Lumbar Drainage	1,14

ICP – Significance (Chi Square). Table 42

Test Statistics. N	21
Chi-Square	36,857
df	2
Asymp. Sig.	,000

ICP Outcome – Pairwise Comparisons. Table 43

Pairwise Comparisons (Sample 1-Sample 2)	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
ICP after Lumbar Drainage-ICP initial	,714	,309	2,315	,021	,062
ICP after Lumbar Drainage-ICP during Lumbar Infusion	1,857	,309	6,018	,000	,000
ICP initial-ICP during Lumbar Infusion	-1,143	,309	-3,703	,000	,001

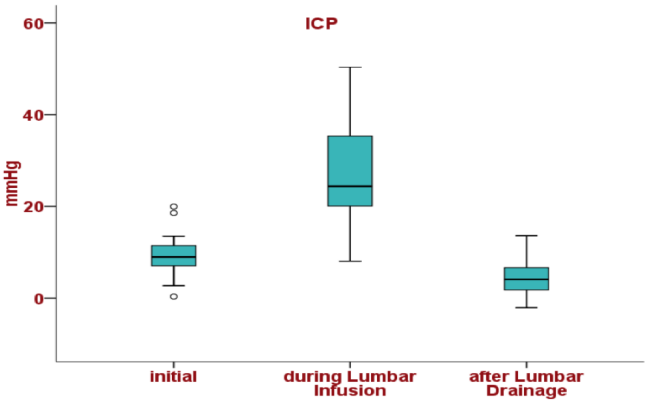


Figure 28: ICP Outcome (Intracranial Monitoring)

These tables (40, 41, 42, 43) and the figure 28 show the outcome regarding the significance of the Intracranial Pressure (ICP) at the three time points when this parameter was measured (Test Initial, during Lumbar Infusion Study and after Lumbar Drainage). The significance of these three time points together (Chi Square) was p<0,001, i. e. the difference was significant and the (H1) was accepted. In the relation between the three time points

separated (Pairwise comparisons) the significance was $p<0.05$ for the three relations (after Lumbar Drainage – Initial Test; after Lumbar Drainage – during Lumbar Infusion Study, and Initial Test – during Lumbar Infusion Study), i. e. the difference was significant and (H1) was accepted. The Figure 28 shows the distribution in the outcome for the ICP.

Slow - Percentile Ranking (ICM). Table 44

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Slow initial	21	1,4968	,51976	,81	2,81	,9950	1,4600	1,7500
Slow during Lumbar Infusion	21	3,1967	1,30202	1,80	7,42	2,4400	2,7700	3,6600
Slow after Lumbar Drainage	21	1,0171	,44964	,35	1,92	,6950	,9200	1,4550

Slow – Friedman Test. Table 45

Friedman Test / Ranks	Mean Rank
Slow initial	1,95
Slow during Lumbar Infusion	2,95
Slow after Lumbar Drainage	1,10

Slow – Significance (Chi Square). Table 46

Test Statistics. N	21
Chi-Square	36,286
df	2
Asymp. Sig.	,000

Slow Outcome – Pairwise Comparisons. Table 47

Pairwise Comparisons (Sample 1-Sample 2)	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
Slow after Lumbar Drainage-Slow initial	,857	,309	2,777	,005	,016
Slow after Lumbar Drainage-Slow during Lumbar Infusion	1,857	,309	6,018	,000	,000
Slow initial-Slow during Lumbar Infusion	-1,000	,309	-3,240	,001	,004

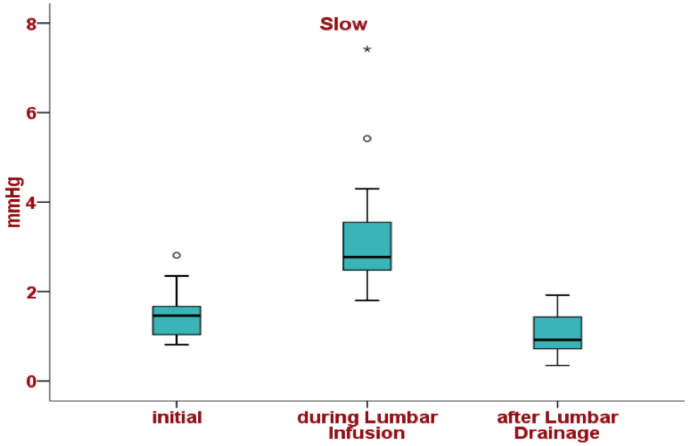


Figure 29: Slow Outcome (Intracranial Monitoring)

These tables (44, 45, 46, 47) and the figure 29 show the outcome regarding the significance of the Slow at the three time points when this parameter was measured (Test Initial, during Lumbar Infusion Study and after Lumbar Drainage). The significance of these three moments together (Chi Square) was p<0,001, i. e. the difference was significant and the (H1) was accepted. In the relation between the three time points separated (Pairwise comparisons) the significance was p<0,05 for the three relations (after Lumbar Drainage – Initial Test; after Lumbar Drainage – during Lumbar Infusion Study, and Initial Test – during Lumbar Infusion Study), i. e. the difference was significant and (H1) was accepted. The figure 29 shows the distribution in the outcome for the Slow. The best outcome is found after Lumbar Drainage.

AMP - Percentile Ranking (ICM). Table 48

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Amp initial	21	2,1210	,68137	1,17	4,13	1,6600	2,0200	2,3400
Amp during Lumbar Infusion	21	6,0981	2,01607	2,98	12,70	5,1600	5,9600	6,8650
Amp after Lumbar Drainage	21	1,2915	,40826	,45	2,06	,9500	1,2200	1,6000

AMP – Friedman Test. Table 49

Friedman Test / Ranks	Mean Rank
Amp initial	1,95
Amp during Lumbar Infusion	3,00
Amp after Lumbar Drainage	1,05

AMP – Significance (Chi Square). Table 50

Test Statistics. N	21
Chi-Square	40,095
df	2
Asymp. Sig.	,000

AMP Outcome – Pairwise Comparisons. Table 51

Pairwise Comparisons (Sample 1-Sample 2)	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
Amp after Lumbar Drainage-Amp initial	,905	,309	2,932	,003	,010
Amp after Lumbar Drainage-Amp during Lumbar Infusion	1,952	,309	6,326	,000	,000
Amp initial-Amp during Lumbar Infusion	-1,048	,309	-3,395	,001	,002

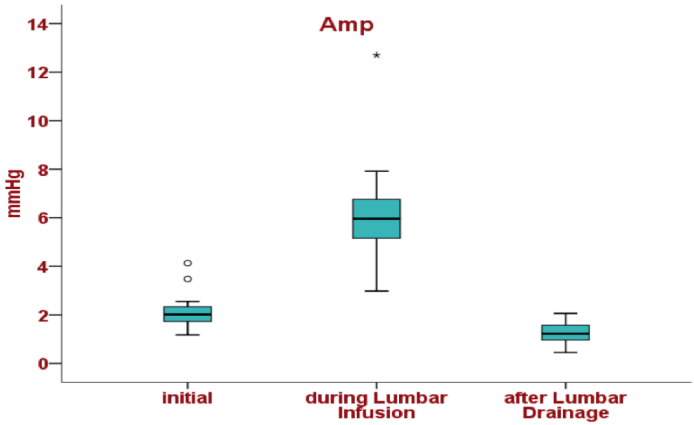


Figure 30: AMP Outcome (Intracranial Monitoring)

These tables (48,49,50,51) and the figure 30 show the outcome regarding the significance of the Amplitude (AMP) at the three time points when this parameter was measured (Test Initial, during Lumbar Infusion Study and after Lumbar Drainage). The significance of these three time points together (Chi Square) was p<0,001, i. e. the difference was significant and the (H1) was accepted. In the relation

between the three time points separated (Pairwise comparisons) the significance was $p<0,05$ for the three relations (after Lumbar Drainage – Initial Test; after Lumbar Drainage – during Lumbar Infusion Study, and Initial Test – during Lumbar Infusion Study), i. e. the difference was significant and (H1) was accepted. The Figure 30 shows the distribution in the outcome for the AMP.

Kiefer Score- Percentile Ranking (Clinical Evaluation). Table 52

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Kiefer-Test initial	21	9,33	4,465	3	22	6,50	8,00	12,50
Kiefer-Test after VP-Shunt	21	7,71	3,989	2	17	4,00	7,00	10,50

Kiefer Score – Wilcoxon Ranks. Table 53

Wilcoxon Signed Ranks Test		N	Mean Rank	Sum of Ranks
Kiefer-Test after VP-Shunt - Kiefer-Test initial	Negative Ranks	14	8,93	125,00
	Positive Ranks	4	11,50	46,00
	Ties	3		
	Total	21		

Kiefer Score Outcome. Table 54

Test Statistics. N	Kiefer-Test after VP-Shunt - Kiefer-Test initial
Z	-1,730
Asymp. Sig. (2-tailed)	,084

One sided Test: 0,084 / 2: p:0, 042 (The Hypothesis is unidirectional)

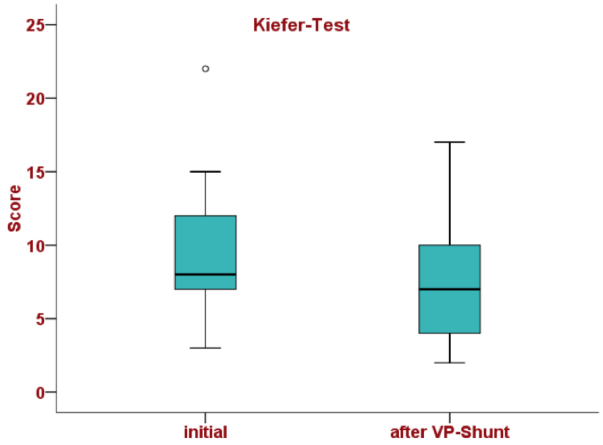


Figure 31: Kiefer Score Outcome (Clinical Evaluation)

These tables (52, 53, 54) and the figure 31 show the outcome regarding the significance of the Kiefer Score at the two moments when

this test was applied (Test Initial and after VP-Shunt Implantation). The significance (according Wilcoxon Signed Ranks Test) was initially p:0,084, but this hypothesis is unidirectional and this value can be divided by 2 (p:0,042), i. e. p<0,05, i. e. the difference was significant and the (H1) was accepted. The Figure 31 shows the distribution in the outcome for the Kiefer Score. A better outcome is found after VP Shunt.

RAP - Percentile Ranking (ICM). Table 55

Descriptive Statistics	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
RAP initial	21	,7137	,13748	,41	,88	,6330	,7100	,8425
RAP after Lumbar Drainage	21	,4493	,19569	,10	,80	,2850	,4400	,6475

RAP – Wilcoxon Ranks. Table 56

Wilcoxon Signed Ranks Test		N	Mean Rank	Sum of Ranks
RAP after Lumbar Drainage - RAP initial	Negative Ranks	20	11,45	229,00
	Positive Ranks	1	2,00	2,00
	Ties	0		
	Total	21		

RAP Outcome. Table 57

Test Statistics. N	RAP after Lumbar Drainage - RAP initial
Z	-3,945
Asymp. Sig. (2-tailed)	,000

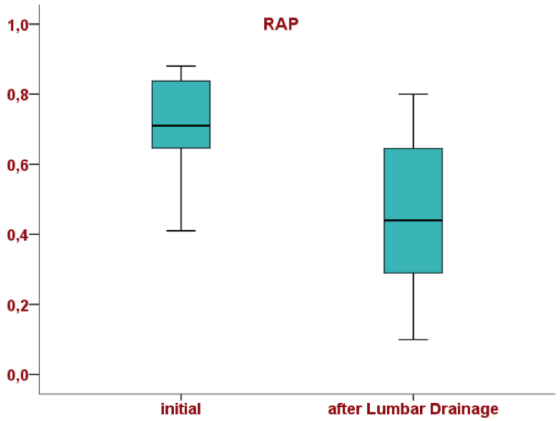


Figure 32: RAP Outcome (Intracranial Monitoring)

These tables (55, 56, 57) and the figure 32 show the outcome regarding the significance of the RAP at the two time points when this parameter was measured (Test Initial and after Lumbar Drainage). The significance (according Wilcoxon Signed Ranks Test) was p<0,001, i.

e. the difference was significant and the (H1) was accepted. The Figure 32 shows the distribution in the outcome for the RAP. The best outcome is found after Lumbar Drainage.

5 Discussion

The results comprise clinical tests applied to patients at the initial evaluation, after 3 days of lumbar drainage and 6 months after VP-Shunt implantation. Furthermore the results ICP overnight monitoring and CSF dynamics during the lumbar infusion test are shown.

This is a highly selected cohort of patients which either failed an initial spinal tap test at an outside institution or department or were recruited from the neurosurgical outpatient clinic. After 3 days lumbar drainage protocol those patients were considered for shunt therapy who either had a clinical improvement in walk test or pegboard test of ≥ 10% plus subjective improvement according to patient or relatives. Alternatively, patients were considered for shunt of their clinical improvement in walk test or pegboard test was 5-10% plus subjective improvement plus one

of the following values of the supplemental tests was present, indicating an decrease in craniospinal compliance: initial overnight monitoring: mean RAP >0,6, mean AMP > 1 mmHg, or R_{out} > 13 mmHg*min^{-1} or PVI <15 ml, or E > 0,15 1/ml.

Patients were only included into the analysis if they received a shunt within 4-8 weeks after testing, to make sure that the clinical status of the patients was still as recorded. In this aging cohort of patients a longer interval might mean that the clinical status could have deteriorated further in the meantime.

The tables on gender and age show an equal sex distribution and most patients were between 70 and 80 years. The mean was 75,43 years (SD: 6,50).

The descriptive statistic representation of all clinical tests (Walk Test, Minimental Test and Pegboard Test) show an improvement for the

whole cohort 6 months after shunt implantation. The Walk Test and Minimental Test showed a clear improvement already after 3 days of Lumbar Drainage, whereas the Pegboard Test was found improved at 6 months after VP Shunt implantation only. Then, however, it was the test with the highest number of excellent improvements (14 /21 patients) compared to the other two tests.

The Pegboard test is a principal test for the evaluation of the visuospatial and viso-constructive perception, besides being a test of medium level cognitive demand [105]. It evaluates perception of a problem, translation in a motor program and hand skills / hand coordination required for complex visuomotor task [4]. The test results of a lower initial improvement rate, however the highest number of excellent improvements after 6 months indicates, that complex systems seem

to react slower to changes after drainage than simpler tasks like walking. Furthermore it indicates that a visuospatial test, which is executed with the hands and thus is independent of other associated degenerative processes like, for example, those of spine and hip / knee joints, might be more robust and independent and thus more reliable for the evaluation after shunting than walking tests.

The Kiefer Score, which is a mostly descriptive score, did only show an improvement tendency, which was not statistically significant and was thus inferior to identify improvement after shunting compared to test with objective data like for example the pegboard test.

Another reason for this difference is the possible higher inter-observer variability of a clinical score with assessment / interview character like the Kiefer score compared to an objective measurement. In this study the

scoring was often performed by different doctors, which introduced a factor of greater variability leading to a lower repeatability as compared to the pegboard or walking test which have a clear definition how to be performed and where variables can be measured in time and steps.

Monitoring parameters:

The patients included in this work showed in addition to clinical improvement after three days of lumbar drainage also ICP derived values thought to be predictive of clinical improvement once CSF is shunted. Three indices of a decreased craniospinal compliance or reserve capacity like elevated RAP, elevated Elastance and reduced PVI were taken into account for patient selection.

The first hypothesis was, that patients responding clinically to 3 days lumbar drainage trial would show indices of lowered intracranial compliance. Mean ICP in this cohort of patients was normal 9,2 mmHg (SD: 4,80). The ICP amplitude (AMP) (calculated as first harmonic after Fourier transformation) would be expected to be in a range of ≤ 1 mmHg at a normal intracranial compliance. However, in keeping with the hypothesis of low compliance, AMP mean was determined to be double that value 2,1 mmHg (SD:0, 68). In all 21 patients the AMP values were > 1 mmHg (see Table 26).

The RAP Index is the correlation coefficient between change of ICP and change of AMP. It is considered a measure of the intracranial reserve capacity [21]. In the physiological situation of a sufficiently large compliance and reserve capacity, with a flat pressure / volume

curve, changes in intracranial pressure will not be closely related to changes in ICP pulse amplitude, since there is a buffering capacity. Thus, the correlation index between ICP and AMP is around 0 or negative.

In a situation of lowered compliance without much reserve capacity, the slope of the pressure/volume curve is steep. Thus, changes in ICP will more likely result in changes of AMP in the same direction which makes the correlation index positive. A threshold of higher than 0.6 is considered to be an indicator of significantly decreased craniospinal compliance [21]. Figure 32 and Table 26 compares the mean RAP index values before and after 3 days lumbar drainage. The mean RAP value during the initial overnight monitoring (deep sleep phase) was 0.71, and 19/21 patients were > 0.6, indicating a low compliance situation. This is in

keeping with the proposed situation in shunt responsive NPH patients according to the reasoning of the hydrodynamic theory, that a lowered intracranial compliance is present.

In keeping with a low compliance situation indicated in the majority of patients during overnight monitoring by higher AMP and RAP, the values of Elastance and PVI, calculated from lumbar infusion study, could have been expected to be high (Elastance) or low (PVI) in those patients as well. However, this was only the case for a little more than 50% of patients and there was no correlation between PVI and Elastance on one hand and RAP/AMP results on the other hand. This indicates, that the data derived from ICP monitoring over a whole night and the results of a volume loading test applied to the spinal compartment within 30-60 minutes are rather two sides of the same coin than measurements of the same component or

system of craniospinal compliance. During a volume load test the compliance parameters are determined by the speed (time) it takes to reach a new plateau. Here on one hand the amount of available intracranial and intraspinal blood, which can be displaced in response to an increase of CSF volume, plus on the other hand the ability of the lumbar dural sac to extend and accommodate additional volume without a larger rise in pressure are the two most likely determinants of Elastance and PVI. Thus there are two spinal contributors. For the RAP determination, however, only intracranially recorded ICP was taken. The ability to displace spinal blood and the influence of spinal dural compliance most likely has a lower influence on the correlation of changes in ICP and changes in AMP. Therefore the lack of correlation - RAP/AMP

on one hand and Elastance and PVI on the other hand - can be explained.

In summary, the first hypothesis that patients which respond clinically to 3 three day lumbar drainage trial also show indices of decreased craniospinal compliance was thus proven valid.

The second hypothesis was, that shunting primarily leads to an increase in intracranial compliance and restoration of reserve capacity by removing CSF. In the descriptive statistics we can see that apart from lowering ICP from the mid normal range to the lower normal range, the values of AMP, RAP and SLOW were significantly changed at the end of the lumbar drainage trial in the sense of a better – higher compliance.

The change in ICP from a mean of 9.2 mmHg (SD: 4,8) to a mean of 4.0 mmHg (SD: 3,9) was rather moderate despite the fact that a

high volume drainage of several hundred ml of ICP was achieved during those three days.

After lumbar drainage the RAP fell from a mean of 0.71 (SD: 0,14) to a mean of 0.45 (SD: 0,2). This reflects the fact, that the removal of CSF by lumbar drainage did not only decrease the ICP but improved significantly the intracranial compliance situation. Most likely, the removal of CSF resulted in an increase of the intracranial blood volume within the venous capacitance vessels, which in turn increased the compliance. Therefore, one conclusion from the lumbar drainage trial is, that a shunt at least as much improves the intracranial compliance situation as it decreases the ICP, Most likely the first effect is the more important one, since the patients have a normal intracranial pressure anyways.

AMP did as well decrease after drainage in keeping with the theory of an increase in compliance from a mean of 2,1 mmHg (SD: 0,68) to a mean of 1,3 mmHg (SD:0, 40). Interestingly, the mean value was still above 1 mmHg, which is considered the threshold for a decreased intracranial compliance, however, now 6/21 patients had a mean AMP < 1 mmHg compared to 0/21 before drainage. In all other patients AMP decreased as well.

In summary, the second hypothesis seems to be valid according to the results after lumbar drainage in this patient cohort.

For the description of the clinical effects after 6 months of shunt therapy we had two options at hand. First, there were the clinical tests performed initially and after 6 months and second all patients were scored with the Kiefer Score, which is a mixtures of description and measurements.

Regarding the clinical tests (Walking test, Pegboard test and Minimental test) an Improvement Index for assessment of change after 6 months of shunt therapy was calculated according to the equation: [(Test-Initial Value – Test-Value 6 Mo. after VP-Shunt / Test-Initial Value) x 10]. An improvement >15% was considered as Excellent, between 10-15% as Good, between 5-10% as Fair and <5% as Poor. This last value includes also all cases of clinical deterioration, which will be shown for each patient in the graphics.

It should be noticed that the results for the three different tests, which measure three different aspects that can be affected by the disease, were different as could be expected.

The test with the greatest number of patients that show an improvement index >15% was the Pegboard Test with a total of 14 of 21 patients, taking one patients with an

improvement of >10%, there were 15 of 21 patients with a sustained improvement at 6 months.

Regarding the Walk-Test half of the patients (12 of 21) showed an improvement index >10%, with 7 having excellent results > 15%.

The test with the greatest number of patients without improvement (index <5%) was the Minimental test with a total of 11 of 21 patients. Further 2 patients had only fair (index <10%) improvement, thus more than 60% of patients did not improve after shunting regarding their Minimental test results.

It is because the iNPH represents a subcortical dementia and not a primary functional cortical disorder [24]. This test provides basically a fast and global measure of the cognitive alteration´s severity and allows to quantify the patient´s degree of cortical dementia [34], [4]. For this reason and in accordance with these

results, the Minimental test is no a good predictor of cognitive response in shunted patients.

The NPH recovery rate was calculated according to the equation: [(Kiefer Initial Value – Kiefer Value 6 Mo. after VP-Shunt / Kiefer Initial Value) x 10]. An improvement ≥7 is considered as Excellent, ≥5 as Good, ≥3 as Fair, ≥ 2 as Transient and <2 as Poor. The long term response after shunt implantation shows that 12 patients were Poor (57%), 4 were Fair (19%), and 5 were Good (24%) in relation to the initial test. There was no patient with a score ≥7, i. e., with an excellent long term response. The outcome 6 months after shunt as assessed with the Kiefer Scale based NPH recovery scale was thus worse compared to the scalable outcome measures. As already discussed above, the Kiefer Scale did not show such significant improvements, probably

due to a high variability in assessment of different doctors at different time points and in consequence the NPH recovery scale showed a much lower rate of improvement. Consequently, the correlation between NPH Recovery Rate in relation to the differences of Intracranial Monitoring results (ICM) after lumbar drainage (ICP, Slow, AMP, RAP) and after lumbar infusion study (E, PVI, R_{out}) was not significant ($p>0,05$) and the (H1) was rejected.

The lineal correlation analysis of intracranial monitoring and lumbar infusion test variables in relation to the improvement in NPH recovery rate showed no or only a weak correlation. This can be explained by the fact that the sample was small and that the clinical results showed a great variability, which represents a disadvantage from a statistical analysis point of view.

The Comorbidity Index (CMI) shows in the descriptive statistics a non gausserian distribution of the sample with 17 patients within the range of 1 – 3 points and 4 Patients within 4 – 7 points. The statistical correlation between Comorbidity Index (CMI) on one hand and, NPH Recovery Rate and the Improvement Indeces (Walk Test, Pegboard Test and Minimental Test) on the other hand showed that there was no correlation between CMI and NPH Recovery Rate and CMI and Walk Test. However, the correlation between CMI and Pegboard Test (p: 0,043) and Minimental Test (p: 0,009) was significant ($p \leq 0,05$). The Minimental Test and Pegboard Test evaluate the cognitive and visual-spatial capabilities of the patient. These tests are objective and less influenced by external factors like orthopedic disorders, which could explain the fact, that here a correlation was

seen but none existed to the walking test. Recent studies state that the CMI plays a predictive role with regard to iNPH patients' postoperative evolution. It is expected that the lower the preoperative CMI score is, the better the prognosis for a postoperative improvement [68]. In this sense, if the CMI score is 6 or greater, a clinical postoperative improvement cannot be expected [68]. According to this, in our study only 2 of 21 patients had a CMI greater than 6. Although both patients had a clinical improvement after the lumbar drainage they did not showed any clinical improvement, when they were controlled 6 months after the VP Shunt implantation. Only one patient of the sample that had more than 4 points at the CMI scale showed a clinical improvement 6 months postoperatively. Concur with Lemcke and Meier [68], these findings underscore the fact that comorbidity is a statistically significant and

a serious negative predictor in the treatment of these patients. The role of CMI as a predictive parameter is related to a variety of pathologies (including vascular risk factors, cerebrovascular disease, peripheral vascular occlusions and others illnesses like Parkinson's disease), their severity, and the medical and psychosocial treatment and also the rehabilitation that the patient receives. There is no doubt that the factors included in the CMI can induce directly or indirectly a rising cerebrovascular resistance and decrease of vascular compliance (loss of Windkessel) which will further enhance the hyperpulsatility already promoted by the decrease of intracranial compliance.

6 Conclusions

The purpose of this work was to demonstrate in patients with suspected iNPH, which are considered as probably shunt responders, that indices taken from ICP monitoring and lumbar infusion study, will be consistent with a coexisting lowered intracranial or craniospinal compliance. The current concept of iNPH involves the idea, apart from being the only variant of dementia disorders possibly treatable by neurosurgical intervention [69], that its pathophysiological process can be explain through a decrease of intracranial compliance (resulting in a complex dysfunction of cerebral blood flow in parallel to a change in CSF dynamics). The second hypothesis was that a three day lumbar drainage protocol would improve intracranial compliance, since our hypothesis was that this is the main effect of a shunt that leads to a clinical improvement.

Both of these hypothesis could be proven by the investigation.

However, we furthermore demonstrated that there was only a weak direct correlation between the intracranial monitoring and lumbar infusion test variables to the improvement in clinical tests. Especially the Kiefer Score and the dependent "NPH recovery rate", which are both subject to a great deal of interpretation of the interviewer, were not well correlated and did not show a comparable improvement as did the more objective outcome measures "walk test" and "pegboard test".

The weak correlation could have also been negatively influenced by the fact that the sample was small and that the clinical results were greatly variable, which represents a disadvantage from a statistical analysis point of view.

We could clearly demonstrate, that patients responding to three days lumbar drainage trial showed indices of lowered intracranial compliance and that shunting these patients primarily leads to an increase in intracranial compliance and restoration for reserve capacity by removing CSF. Therefore we suggest, that the combination of computerized analysis of intracranial pressure and cerebrospinal fluid dynamics with the lumbar infusion test and three days lumbar drainage represent, although an extensive procedure, the most accurate way to diagnose shunt responsive idiopathic normal pressure hydrocephalus. Future research needs to be directed towards a simplification of the diagnostic procedures without loosing the diagnostic accuracy. This dissertation, besides trying to demonstrate the importance and usefulness of the invasive techniques and

diagnosis protocols in dealing with iNPH, furthermore has a large introductory section on the theoretical foundations of the current theories regarding a low compliance situation with intracranial hyperpulsatility. Despite its length and extend, this section demonstrates the extensive work undertaken in the attempt to understand and elucidate as much as possible the theoretical background of a complex pathophysiology.

7 Zusammenfassung und Ausblick

Ziel dieser Arbeit war, bei Patienten mit idiopathischem Normaldruckhydrocephalus (iNPH), die als potentielle „Responder“ einer Therapie mit einem ventrickulo-peritonealen Shunt angesehen werden, mit Hilfe invasiver Methoden (computerisierte nächtliche Hirndruckanalyse und lumbale Infusionsstudie) nachzuweisen, dass eine erniedrigte intrakranielle Compliance vorliegt. Die momentan besterklärende pathophysiologische Hypothese zum iNPH geht davon aus, dass der Erkrankung eine über die erniedrigte Compliance bedingte Pulsatilitätsstörung von Blut und Liquor mit assoziierter Beeinträchtigung des zerebralen Blutflusses zugrunde liegt.

Die 2. Hypothese der Arbeit war, daß eine dreitägige Lumbaldrainage, die zu einer

klinischen Verbesserung des Patienten führt, mit einer Zunahme der intrakraniellen Compliance und Verbesserung der Reservekapazität einhergeht. Dies würde unsere Auffassung stärken, dass der wesentliche Effekt der Shunttherapie über die Verbesserung der Compliance vermittelt wird. Beide Hypothesen konnten in der Arbeit bestätigt werden.

In Bezug auf die Korrelation des klinischen Scores (Kiefer Scale und der darauf basierenden NPH Recovery Rate) fanden wir keine überzeugende Korrelation zum Ausmaß der Besserung und dem Ausmaß der Veränderung der compliance assoziierten Messwerte. Neben der kleinen Patientenanzahl ist dies wahrscheinlich darin begründet, dass der Kiefer Scale unscharfe und subjektive Einschätzungen von Patient

und Arzt beinhaltet. Eine deutlich bessere Korrelation fand sich zu objektiven Messverfahren wie Gangtest und Pegboard Test.

Zusammenfassend konnte die Arbeit nachweisen, dass bei Patienten mit vermutetem iNPH eine erniedrigte cranio-spinale Compliance assoziiert ist mit einem guten Ansprechen auf eine dreitägige Liquorprobedrainage und nachfolgend einer Shunttherapie , und, dass die dabei bewirkte Entfernung vom Nervenwasser zu einer Erhöhung der intrakraniellen Compliance führt. Daraus folgt, dass die Kombination einer computerisierten Analyse des intrakraniellen Druckes und der cerebrospinal Liquordynamik (lumbale Infusionsstudie) eine aufwändige aber präzise pathophysiologisch orientierte Methode der Diagnose von jenen

Normaldruckhydrocephalus Patienten ist, bei denen eine klinischen Verbesserung nach Shunt Implatantion zu erwarten ist. Zukünftige Arbeiten sollten zum Ziel haben, eine Simplifizierung der Diagnostik bei gleichbleibenden Aussagekraft, idealerweise unter Verwendung weniger invasiver Verfahren, zu erreichen.

8 List of Tables

9 List of Figures

10 Bibliography

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Declaration of Authorship

I, Jordana Mag Lui Sosa Carrero, (born an 15.03.1980 in Maracay, Estado Aragua, Venezuela) declare that this dissertation with the title: “Computerized analysis of intracranial pressure and cerebrospinal fluid dynamics in patients with idiopathic normal pressure hydrocephalus and positive clinical response to lumbar CSF drainage“ has been written by me and that I have not used prohibited or illegal sources for its composition. The data used both in theoretical and practical aspects have been rightly collected according to medical ethics and showing respect for copyrights. The statistics analyses has been performed and written by me.

These thesis was performed at the University Clinic of Tübingen in the Service of

Neurosurgery in the Clinic of Neurosurgery under tutorial guidance of Prof. Dr. Martin U. Schuhmann.

Jordana Mag Lui Sosa Carrero

Tübingen, March 2017

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