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Hydrocephalus
Water on the Brain

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HYDROCEPHALUS - WATER ON THE BRAIN

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http://dx.doi.org/10.5772/intechopen.69908
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Notice

First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Hydrocephalus - Water on the Brain
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p. cm.

Print ISBN 978-1-78923-486-2

Online ISBN 978-1-78923-487-9

eBook (PDF) ISBN 978-1-83881-438-0

Meet the editor

Bora Gürer was graduated from the Dokuz Eylul University, Faculty of Medicine, in 2007. He then started his neurosurgical residency at the Ankara Diskapi Education and Research Hospital. He spent 6 months as a fellow at the University of Wisconsin, Department of Neurosurgery. After completing his residency program in 2013, he passed national exams and assumed the title of associate professor of Neurosurgery. He is currently affiliated to the Department of Neurosurgery, University of Health Sciences, Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey. Besides being the youngest associate professor of Neurosurgery in his country, he has a keen interest in complex neurovascular, neurooncological, and skull base surgeries.

Contents

Preface

With eight chapters, this book provides in-depth details of the symptomatology, physiology, and medical and surgical treatments of hydrocephaly. As a modern treatment modality of hydrocephaly, endoscopic third ventriculostomy occupies a respectable space in this book.

In this book, many experts share their experience and knowledge on different aspects of hydrocephaly, including anatomy, physiology, and medical and surgical treatments. This book will be of interest and provide detailed information for those involved in the management of patients with hydrocephaly.

I would like to thank all the authors who have contributed to this project. Also, I would especially like to thank all kind of people from IntechOpen author services.

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Introduction

Chapter 1

Introductory Chapter: History of the Hydrocephaly

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77371

1. Introduction and the history of hydrocephaly

In the modern era of medicine, the term hydrocephaly (from Greek hydro = water + kefale = head) indicates an excessively increased volume of cerebrospinal fluid (CSF) with dilated ventricle system.

The first physician who documented the hydrocephaly was Hippocrates (fifth century BC), the father of medicine. Furthermore, he attempted to treat with subdural or subarachnoid punctures. In the works of Galen (130–200 AD), one can find footprints of the hydrocephaly, as he believed the condition occurred from the accumulation of the fluid in the extra-axial spaces. As descendants of Hippocrates and Galen, many ancient Greek physicians reportedly treated hydrocephaly by trephined openings to the skull [1].

At the University of Padua, Vesalius (1514–1564) was first to report that "the water had not collected between the skull and its outer surrounding membrane, but within the ventricles of the brain" [2].

Thomas Willis, in 1664, was first to come up with the idea that CSF is produced by choroid plexus of the ventricles [3]. In 1774, Cotugno demonstrated that ventricles were filled with fluid during fluid during lifer and he successfully aspirated the fluid via percutaneous methods [4]. Till to modern era, the pathophysiology of hydrocephaly was poorly understood and initial therapeutic attempts were generally failed.

As human kind technologically developed, in the twentieth century, physiology of CSF dynamics and pathological mechanisms causing hydrocephaly have more definitely determined. This new knowledge caused the discovery of more rational and radical treatments. In 1891, Quincke was first to describe lumbar puncture as an effective treatment for hydrocephaly. Continuous ventricle drainage was primarily performed by Keen. Attempt to drain

ventricular CSF to the subgaleal, subdural, and subarachnoid spaces was being tried by Miculicz firstly with the use of gold tubes and catgut strands [5].

Balkenstich method, which the callosotomy was performed to drain lateral ventricle to the subdural space, was introduced by Anton and von Bramann. Unfortunately, this procedure was withdrawn due to high mortality rates [6].

In 1908, by using vein grafts, Payr created a drainage corridor between the ventricles and sinus sagittalis superior or jugular veins [7]. In the very same year, Kausch performed ventriculoperitoneal drainage system with rubber tubes [8].

In the same period, Heile performed several spinal CSF diversions to the peritoneum and urinary system with various methods [9].

As a pioneer neurological surgeon, Cushing also described a technique of lumboperitoneal CSF diversion by silver cannulas via L4 vertebral corpus [5].

Dandy was reported that CSF production was made grossly by choroid plexus and this in turn led Dandy to introduce bilateral choroid plexectomy to reduce CSF production [10]. To treat infantile hydrocephaly, this method had been used as a procedure of first choice in the United States. Endoscopic choroid plexectomy followed this development in the late 1930s [11]. Dandy also innovated the lamina terminalis penetration to the third ventricle via subfrontal or subtemporal approaches. This technique was further developed by endoscopic approaches.

Takildsen developed a shunt system between lateral ventricle and cisterna magna (ventriculocisternostomy). By the time, efforts of CSF diversions to other body cavities, such as ureter, heart, jugular vein, thoracic duct, pleural space, gallbladder, fallopian tube, ileum, and salivary ducts had developed [5].

In 1952, Nulsen and Spitz worked with John Holter, whose child also suffering from hydrocephaly, introduced valve-regulated shunt system with spring and ball valve [5]. At the same time, Pudenz produced one-way slit valve from silicone [1]. Ventriculoperitoneal shunt systems were popularized by the attempts of Ames [12] and Raimondi and Matsumoto [13]. Since then, new hardwares were developed. Nowadays, there are numerous options for valves, catheters, antisiphon devices, programmable valves for CSF diversion procedures.

Past three decades, neuroendoscope once again gained popularity, the benefits of which include accurate placement of ventricular catheter and third ventriculostomy [14]. Furthermore, stereotactic localization and neuronavigation secured the procedures and warrant exact localization of ventricular catheters.

2. Conclusion

Despite those technological developments, treating a hydrocephalic patient still remains a challenging procedure for present neurological surgeons. We, neurological surgeons, still

continue to face with numerous, inevitable complications of procedures performed to treat hydrocephaly. As my mentor always mentioned "if you shunted a patient, you solemnize a marriage with her or him".

This book will provide vulnerable knowledge to whom dealing with challenging hydrocephaly.

Conflict of interest

None.

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Section 2

Basic Science Behind Hydrocephaly

Chapter 2

Visualization and Characterization of Cerebrospinal Fluid Motion Based on Magnetic Resonance Imaging

Satoshi Yatsushiro, Saeko Sunohara, Hideki Atsumi, Mitsunori Matsumae and Kagayaki Kuroda

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73302

Abstract

Purpose: To characterize cardiac- and respiratory-driven cerebrospinal fluid (CSF) motions in intracranial space noninvasively, four-dimensional velocity mapping (4D-VM), correlation mapping, and power and frequency mapping with cardiac-gated and/or asynchronous magnetic resonance (MR) phase contrast (PC) techniques were conducted.

Methods: Cardiac-gated PC in three spatial directions was applied to young, healthy, elderly, healthy, and idiopathic normal pressure hydrocephalus patient groups. 4D-VM was created from time-resolved 3D velocity distribution represented as vector and color coding. The curl and pressure gradient were calculated. Correlation mapping provides propagation delay and correlation of CSF motion at arbitrary points regarding a reference point. In addition, asynchronous PC technique was conducted for healthy volunteers with respiratory instruction as constant rhythm. Cardiac- and respiratory-driven velocities were separated by frequency analysis. Power and frequency mapping present both the energy and dominant frequency of cardiac or respiratory CSF motion.

Results: 4D-VM, curl, pressure gradient images, and correlation mapping by cardiac-gated PC demonstrated cardiac-driven CSF motion and its propagation properties. Power and frequency mapping, correlation mapping, and displacement analysis exhibited that the cardiac-driven CSF velocity was higher than the respiratory, although the cardiac-driven displacement was smaller.

Conclusion: Visualization and characterization techniques based on PC imaging can capture the properties of CSF motion in intracranial space.

Keywords: MRI, phase contrast, cerebrospinal fluid, motion, visualization

1. Introduction

Investigations of CSF motion based on MRI have been actively performed [1–6]. CSF motion is thought to be composed of three components: cardiac-driven motion, respiratory-driven motion, and bulk flow [7, 8]. Cardiac-driven motion is primarily induced by arterial blood vessel pulsation and relates to the regulation of intracranial pressure (ICP) [2, 4, 9, 10]. A change in intrathoracic pressure caused by respiration induces the modulation of venous blood pressure, resulting in respiratory-driven motion [6, 11–14]. Bulk flow is a slow motion relating to CSF production and absorption, thus playing a role to washout wastes from the brain through the glymphatic system [7, 8, 15, 16].

Hydrocephalus is the most commonly known disease relating to the alternation of CSF dynamics through, for example, a velocity increase in the aqueduct [17–19]. Although hydrocephalus increases intracranial pressure (ICP) in some cases, normal pressure hydrocephalus (NPH), including idiopathic NPH (iNPH), does not increase ICP, and thus, it is difficult to know the exact status of the disease using invasive pressure measurement, as in a lumber puncture (LP) procedure. Even in such a case there might be abnormality in the CSF dynamics. Therefore, the investigation of the relationship between hydrocephalus and CSF motion is essential. It is also known that the development of Alzheimer's disease (AD) relates to the accumulation of amyloid beta protein and thus to the malfunction of the glymphatic system, which in turn the bulk flow [8]. Thus, the characterization of the CSF dynamics may lead to the key for clarifying the status and the symptom of the abovementioned diseases.

This chapter presents the techniques for the visualization and characterization of CSF motion in intracranial space based on the cardiac-gated PC [20, 21] and asynchronous PC technique of MRI.

2. Material and methods

The use of human subjects in this study was approved by both internal review boards of Tokai University, Kanagawa, Japan, and Tokai University Hospital, Kanagawa, Japan. All volunteers were examined after appropriate informed consent was obtained.

2.1. Cardiac-gated and asynchronous PC techniques

The cardiac-gated PC technique is the combination of continuous PC acquisition and retrospective reconstruction. A schematic diagram of the cardiac-gated PC acquisition is explained in **Figure 1(a)**. The signal is read out regardless of the electrocardiography (ECG) signal. The signals are sorted retrospectively according to the delay time from the R-wave of ECG signal to form a time series of k-space images. The k-space series are then reconstructed to be multiple PC images resulting in time-resolved velocity images. In this technique, the respiratory-induced motion is simply ignored.

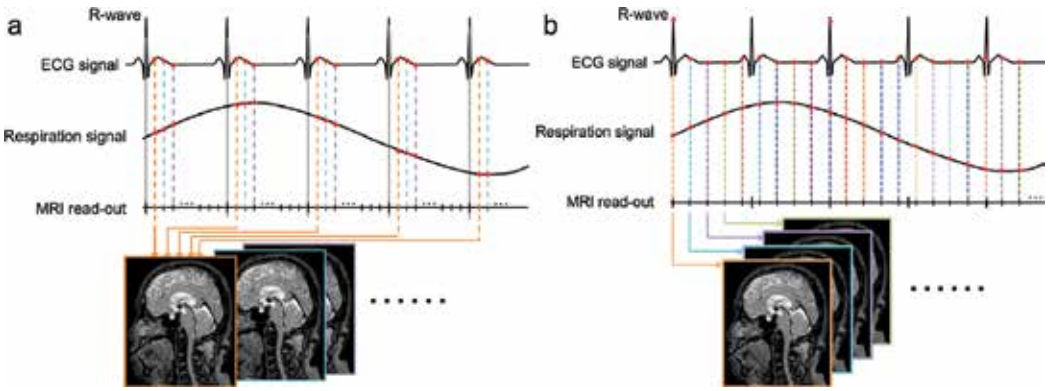

Figure 1. Schematic diagram of cardiac-gated (a) and asynchronous (b) PC acquisitions.

The asynchronous PC technique uses a rapid signal acquisition scheme, such as steady state free precession (SSFP), to obtain velocity images with the order of 217 ms per frame. When combined with the ECG and respiratory signals monitored during acquisition, this technique may simultaneously measure the cardiac- and respiratory-driven CSF velocities.

2.2. CSF motion visualization based on cardiac-gated PC imaging

Cardiac-gated PC velocity measurement was performed in three spatial directions at 1.5 T for 13 young, healthy volunteers (8 males and 5 females with mean ± SD age of 29 ± 5); 13 elderly, healthy volunteers (4 males and 9 females with mean ± SD age of 72 ± 8); and 13 patients with iNPH (2 males and 11 females with mean ± SD age of 75 ± 5). Detailed imaging conditions are shown elsewhere [10].

In segmenting the CSF space from the T2-weighted images with relatively large voxel size (approximately 1 mm^3) [22], the spatial-based fuzzy clustering method (SFCM) was applied to reduce the possible partial volume effect [23]. This method differentiated tissues with different signal intensities even in an identical voxel and determined the boundary between the tissues, resulting in a reasonably segmented image.

2.3. Four-dimensional velocity mapping

Four-dimensional velocity mapping (4D-VM) visualizes the cardiac-driven CSF motion in intracranial space, which is composed of cardiac-gated PC acquisition in three spatial directions. In-plane velocities were indicated as arrows, while out-plane velocities were color-coded. The time-resolved velocity maps or 4D-VM were superimposed on T2 images.

2.3.1. Curl of the velocity field

In general, a vector field is fully characterized by the divergence and curl of the velocity field based on Helmholtz's theorem [24]. The curl of the velocity field was calculated as follows to provide the intensity of the vortex:

$$curl\ \mathbf{v} = \nabla \times \mathbf{v} \tag{1}$$

where **v** is the velocity vector fields in the spatial directions and ∇ is a spatial differential operator called nabla.

2.3.2. Pressure gradient

The pressure gradient was calculated based on the Navier-Stokes equation as follows:

$$\nabla P = -\rho\left(\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v}\cdot\nabla)\mathbf{v}\right) + \mu\nabla^2\mathbf{v} \tag{2}$$

where ∇P is the pressure gradient [Pa/m]; ρ is the fluid density [kg/m^3], which is 1.007×10^3 in the case of the CSF; and μ is the dynamic viscosity [Pa s], 1.1×10^{-3} for CSF. The first term in the right-hand side of the equation is composed of acceleration. The second is of convection, and the third is of viscosity. Although the pressure gradient is a vector, the absolute of the pressure gradient vector was mapped as color-scale for simplicity.

2.4. Correlation mapping

Correlation mapping is a technique to provide the delay and correlation of CSF motion propagation in space. This technique works under the assumptions that CSF moves with pressure propagating from the pulsation of blood vessels and/or brain parenchyma and that CSF itself is a media of such pressure propagation.

The velocity waveform of CSF motion or blood flow obtained by the time-resolved PC acquisition was sampled at a particular reference point. By time shifting the velocity waveform at an arbitrary point to have the highest correlation coefficient with that at the reference, as illustrated in **Figure 2**, two important parameters, $d_{\max}$ and $P_{d_{\max}}$ may be calculated. The following equation was used to calculate these values assuming that the lengths and shapes of the waveforms are similar to each other and that there is a linear delay between the waveforms:

$$P_d = \frac{\sum_{k=1}^{N}\left(v_{R_k} - \overline{v}_R\right)\left(v_{A_{k-d}} - \overline{v}_A\right)}{\sum_{k=1}^{N}\sqrt{\left(v_{R_k} - \overline{v}_R\right)^2\left(v_{A_{k-d}} - \overline{v}_A\right)^2}} \quad d = (0, 1, 2, \cdots, N-1) \tag{3}$$

where P_d is the correlation coefficient with the number of delay time points d within a cardiac period, v_{R_k} is the velocity of the reference waveform, $\overline{v}_R$ is the average of v_{R_k}, $v_{A_{k-d}}$ is the velocity at the arbitrary spatial location and shifted for d points with respect to the original, $\overline{v}_A$ is the average of $v_{A_{k-d}}$, k is the time index, and N is the total number of data points and thus the number of images, within a cardiac period. Eq. (3) is similar to but different from that used in the pulsatility-based segmentation (PUBS) [25]. The delay giving the maximum correlation

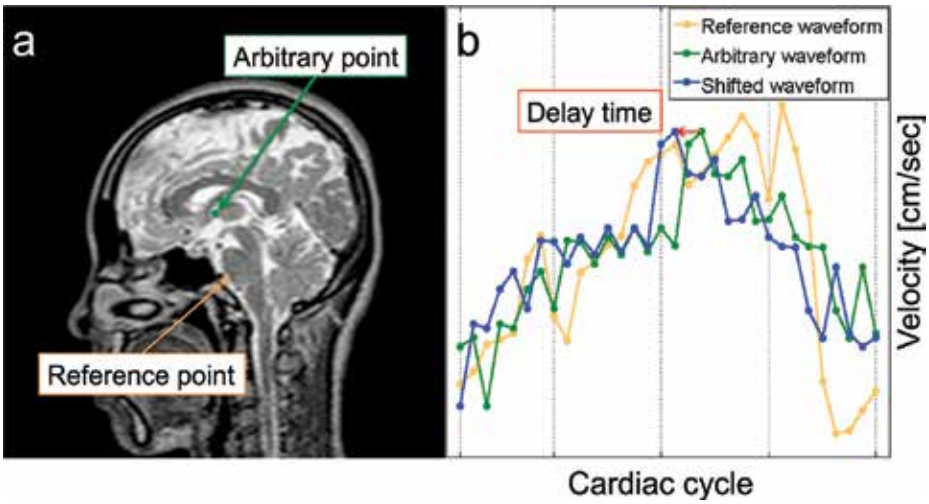

Figure 2. A reference point and an arbitrary point for observing a correlation of CSF velocity waveforms are shown on a T_2-weighted image (a). A waveform at an arbitrary point (green line) was shifted (blue line) to maximize the correlation coefficient with that of the reference (orange line) as shown in (b). The amount of the shift indicated by an arrow was defined as the "delay time," whereas the maximum correlation value was defined as the "maximum correlation."

$P_{d_{\max}}$ was defined as the delay time $d_{\max}$, Then $d_{\max}$ and $P_{d_{\max}}$ were estimated and mapped for all voxels in the CSF space.

After validating the appropriateness of the correlation mapping technique in a flow phantom [10], it was applied to three subject groups. The reference region was set at CSF near the basilar artery in the midline slice to visualize CSF motion propagation derived from the cardiac pulsation [9]. The CSF motion propagation in the FH direction was analyzed because the dominant motion was expected to be to and fro in this direction.

2.5. Cardiac- and respiratory-driven CSF motion characterized by asynchronous PC imaging

Asynchronous 2D-PC imaging in the sagittal plane in the midline was applied to 12 healthy volunteers (10 males and two females with mean ± SD age of 31 ± 13 years old) using 3 T-MRI. Each volunteer was instructed to have 6-s cycle by homemade audio guidance. In addition, 10- and 16-s cycle respiration was also instructed for seven healthy volunteers (six males and one female with mean ± SD age of 31 ± 12 years old). Cardiac and respiratory signals were measured by ECG and a bellows-type pressure sensor on the volunteer's abdomen. Detailed imaging conditions can be found elsewhere [13]. Non-gated, PC image acquisition with 217-ms (4.61 frame/s) temporal resolution was repeated 256 times, resulting in about 56-s total acquisition time for each volunteer.

2.6. Power and frequency mapping

Since cardiac- and respiratory-driven CSF motions have different frequency ranges corresponding to cardiac pulsation and respiration, these motions should appear as different spectral peaks in the frequency domain. Monitoring an ECG signal as well as a respiratory signal, which

is obtained by a bellows-type pressure sensor, the cardiac- and respiratory-driven CSF velocity components were separately extracted in the frequency domain. The energy of the cardiac and respiratory component was calculated by integrating the power spectral density of these components in each voxel and then normalized by the entire energy in the 0–2.0-Hz range. Such calculations were performed for all the voxels including CSF to create a power map (P-map). The frequencies of the maximum peak in the PSD were depicted at all the voxels to form a frequency map (F-map). The brightness of the F-map was weighted with that averages the maximum values of PSD in intracranial space. To quantify the P-map, regions of interest (ROIs) were placed, as shown in **Figure 3**.

2.7. Pressure gradient

The pressure gradient of the cardiac- and respiratory-driven CSF velocity along the FH direction was calculated based on Eq. (2). The average of the positive (caudal-to-cranial) and negative (cranial-to-caudal) peak pressure gradient was quantitatively analyzed in ROIs.

2.8. Correlation mapping

The correlation mapping technique described in the previous section was applied to the cardiac and respiratory velocities of individual volunteers with the reference region set at the spinal subarachnoid space. The maximum correlation and delay time of each motion component were obtained at the ROIs located at the prepontine, aqueduct, fourth ventricle, and lateral ventricle.

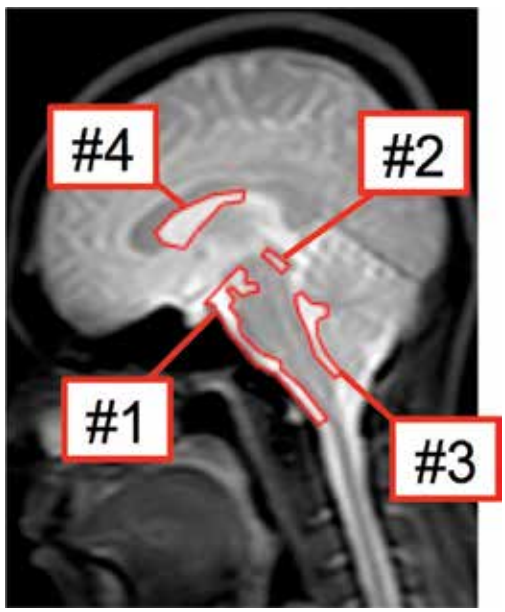

Figure 3. A T2 image of a healthy subject with ROIs: (#1) the anterior cistern of the brainstem, (#2) aqueduct, (#3) fourth ventricle, and (#4) lateral ventricle.

2.9. Displacements of cardiac- and respiratory-driven CSF motion

The displacements of the cardiac and respiratory velocity waveforms were calculated. The displacement was regarded to be during the diastolic or inhalation period when a slope of the velocity waveform was positive and to be during the systolic or exhalation period when a slope was negative. Thus, the displacements were calculated with following equations in the ROIs specified above:

$$D_{dia/inh} = \frac{1}{N}\sum_{n=1}^{N}\left(\sum_{m=1}^{M_{dia/inh}} \left|v\left(m\cdot\Delta t\right)\right|\Delta t\right)_n \tag{4}$$

$$D_{sys/exh} = \frac{1}{N}\sum_{n=1}^{N}\left(\sum_{m=1}^{M_{sys/exh}} \left|v\left(m\cdot\Delta t\right)\right|\Delta t\right)_n \tag{5}$$

where $D_{dia/inh}$ is the CSF displacement during diastole or inhalation, $D_{sys/exh}$ are the displacement during systole or exhalation, $M_{dia/inh}$ and $M_{sys/exh}$ are the number of data points during each physiological state, N is the number of cardiac or respiratory cycles in the observation duration, v is cardiac- or respiratory-driven CSF velocity, and Δt is the temporal resolution.

3. Results

3.1. CSF motion visualization based on cardiac-gated PC imaging

The Reynolds number in the aqueduct was calculated to be around 136 when the velocity was 2.47 cm/s. Since this value was less than 2000, the CSF motion inside the aqueduct was regarded to be a laminar flow when moving toward one direction. The 4D-VM images of the cardiac-driven CSF motion of a healthy volunteer and iNPH patient are shown in **Figure 4**, demonstrating the difference in the velocity distribution between the healthy volunteer and the iNPH patient. The peak-to-peak velocity in the healthy volunteers in the aqueduct was 1.25 ± 0.78 [cm/s], while that in the iNPH patients was 2.86 ± 1.39 [cm/s]. The curl images in **Figure 5** showed that the disturbance around the brainstem in the iNPH patient was higher than that of the healthy volunteer. The intensity of the aqueduct curl was 3.32 ± 1.63 $[(\text{s cm}^2)^{-1}]$ in the healthy volunteers and 14.00 ± 6.87 $[(\text{s cm}^2)^{-1}]$ for the patients. The pressure gradient images in **Figure 6** revealed that the pressure gradient in the iNPH patient around the brain stem was larger than the healthy. In the same region, the pressure gradient was 147.04 ± 97.48 [Pa/m] for the healthy volunteers and 615.66 ± 397.46 [Pa/m] for the patients.

The delay time and maximum correlation maps in **Figure 7** exhibited that the delay and maximum correlation maps for a young, healthy subject differed according to the CSF motion propagation. The result for an elderly, healthy subject looked like similar but slightly different in longitudinal cerebral fissure from the young, healthy subject.

The velocity waveforms obtained from the prepontine, foramen magnum, third ventricle, fourth ventricle, lateral ventricle, and longitudinal fissure, and those power spectra are shown

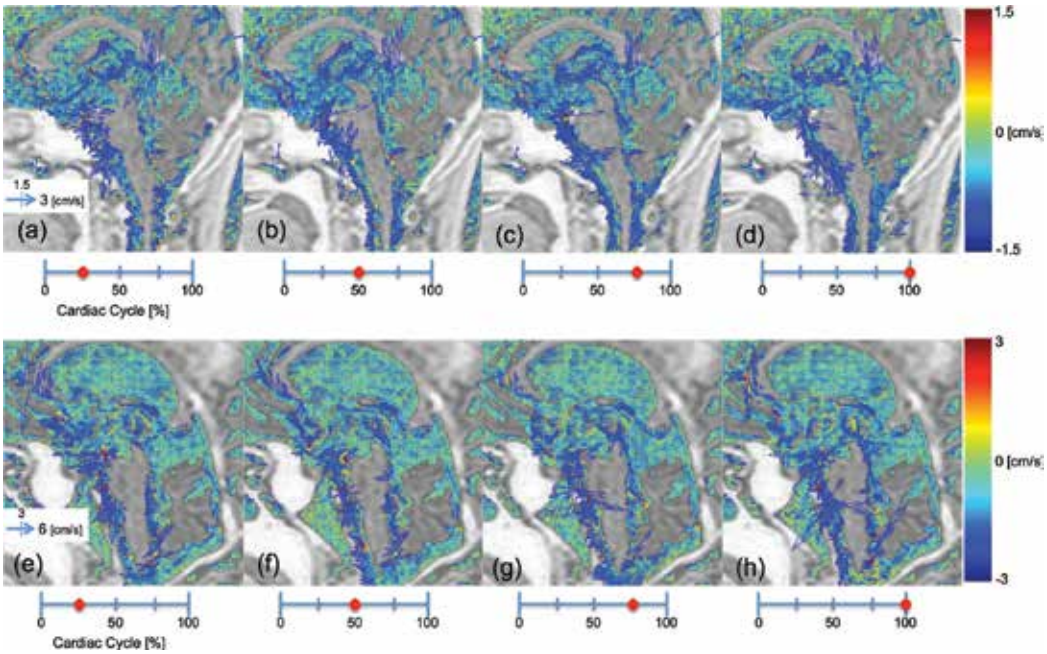

Figure 4. Four-dimensional velocity images of the cardiac-driven CSF motion of a healthy volunteer (a–d) and an iNPH patient (e–h) in a cardiac cycle.

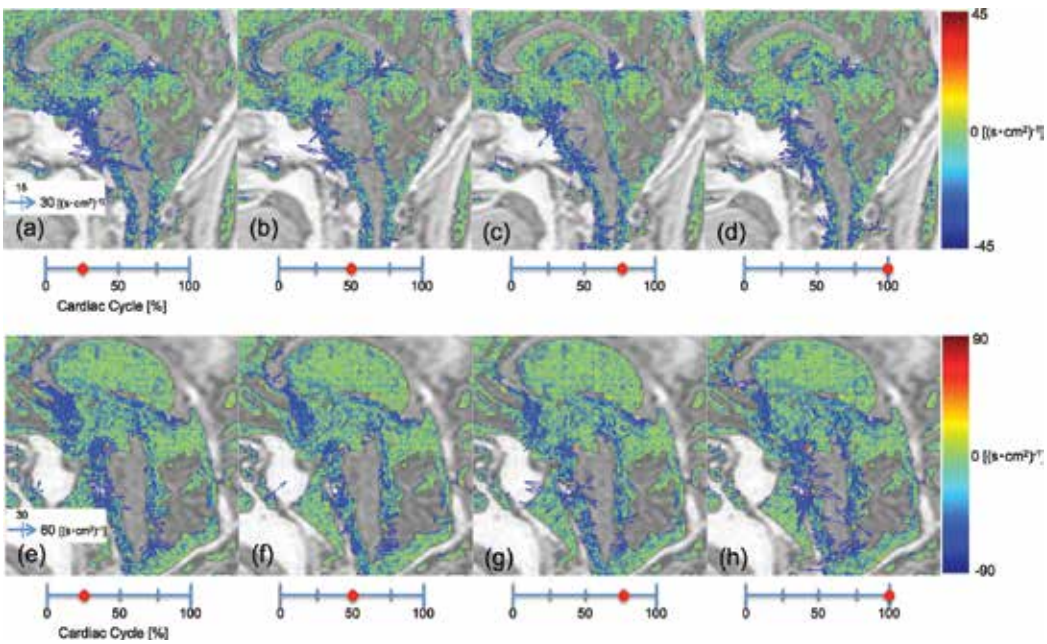

Figure 5. Curl distributions of the cardiac-driven CSF motion of a healthy volunteer (a–d) and an iNPH patient (e–h) in a cardiac cycle.

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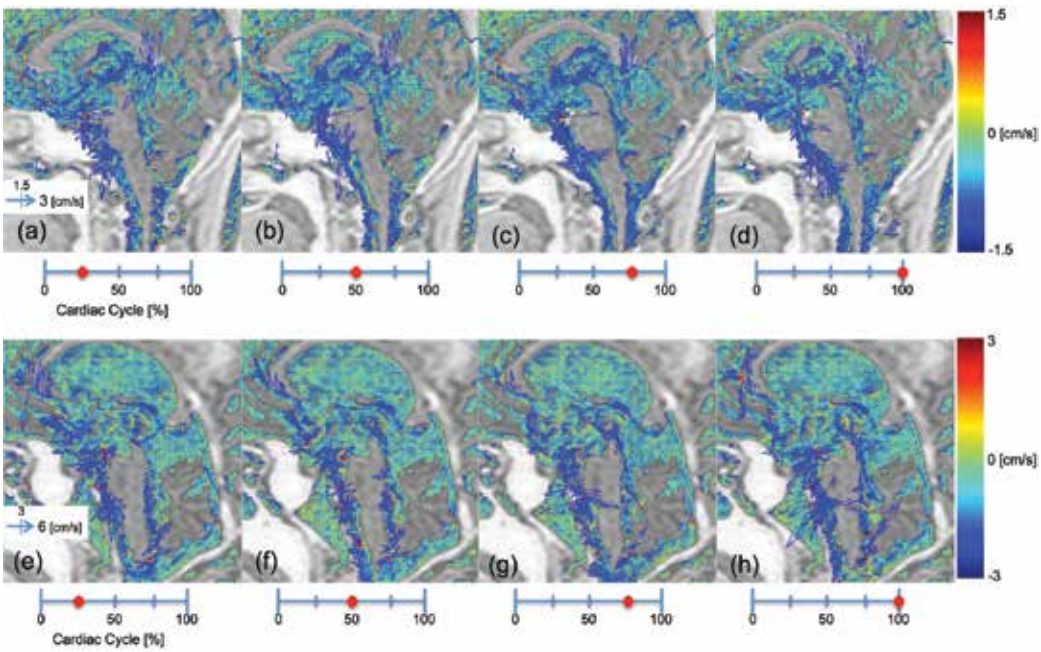

Figure 6. Pressure gradient of the cardiac-driven CSF motion of a healthy volunteer (a–d) and an iNPH patient (e–h) in a cardiac cycle.

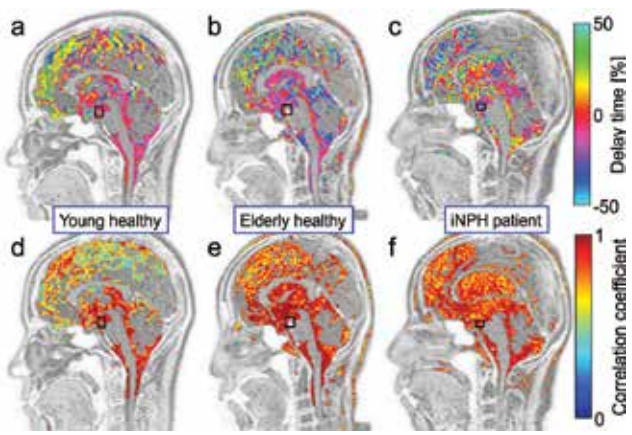

Figure 7. (a–c) are delay time maps, and (d–f) are maximum correlation maps. The black rectangles indicate the reference region. The delay and maximum correlation maps demonstrated propagation properties of CSF motion with different status.

in **Figure 8**. The dominant frequency of the motion in the regions was identical to the cardiac pulsation frequency (≈1.08 Hz). The delay times at the ROIs without the foramen magnum and longitudinal cerebral fissure were quantified, while the mean deviation of the delay was calculated and is summarized in **Table 1**. The mean deviation exhibited a difference of CSF motion propagation among the three subject groups.

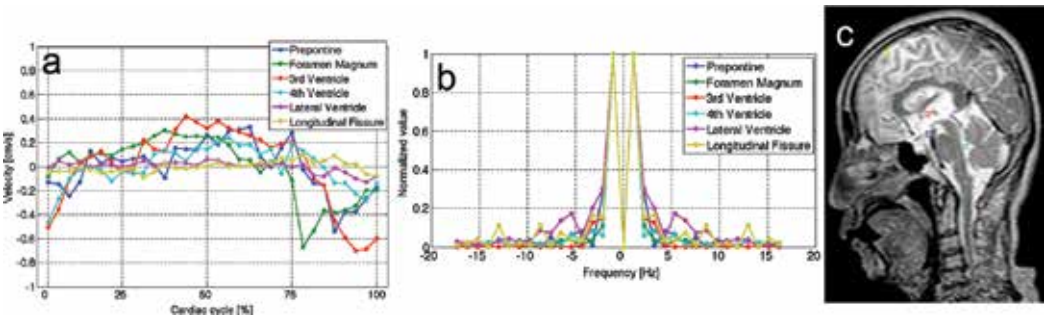

Figure 8. Results for the primary frequency components of the CSF motion propagation. (a) Velocity waveforms are shown at various tissue regions indicated by color squares on T2 image (c). (b) Power spectra of those waveforms normalized by each peak are exhibited.

	Prepontine	Third V[a]	LV[b]	Fourth V[c]	MD[d]
Young, healthy	0.90 ± 2.61	7.03 ± 6.47	12.01 ± 7.69	10.18 ± 9.41	14.25
Elderly, healthy	−0.37 ± 2.82	5.02 ± 6.05	4.56 ± 6.99	5.22 ± 11.86	7.96
iNPH	−0.59 ± 3.88	2.24 ± 3.41	0.92 ± 5.36	2.75 ± 4.41	4.65

[a]Third V, third ventricle
[b]LV, lateral ventricle
[c]Fourth V, fourth ventricle
[d]MD, mean deviation. The rightmost column is the MD of the delay time fraction among the different regions, indicating the variety of the delay time in the intracranial space in each subject group.

Table 1. Fraction of the delay time [%] of CSF motion propagation in a cardiac cycle at the prepontine, third ventricle, lateral ventricle, and fourth ventricle.

The quantification of the average and standard deviation of the maximum correlation coefficient distribution in the intracranial CSF space segmented by the SFCM with manual segmentation is shown in **Figure 9**. Significant differences between the young, healthy group and the others are shown; in addition, the standard deviation of the maximum correlation distribution in the same region indicates significant differences among all groups.

3.2. Cardiac- and respiratory-driven CSF motion characterized by asynchronous PC imaging

Figure 10(a) presents the CSF velocity waveform at a voxel obtained by asynchronous 2D-PC imaging; **Figure 10(b)** is power spectra of the CSF (blue line), ECG (red), and respiratory signal (green); and **Figure 10(c)** is the separated cardiac and respiratory CSF velocities. **Figure 11** represents the cardiac and respiratory P-maps as well as F-map of a healthy volunteer under a 6-s respiratory cycle. The cardiac components were high at the spinal subarachnoid space and anterior cistern of brainstem, while the respiratory components were relatively small in same regions. The F-map showed that the cardiac component around 1 Hz was dominant at the anterior cistern of the brainstem, while various frequencies were intermixed at the frontal horn

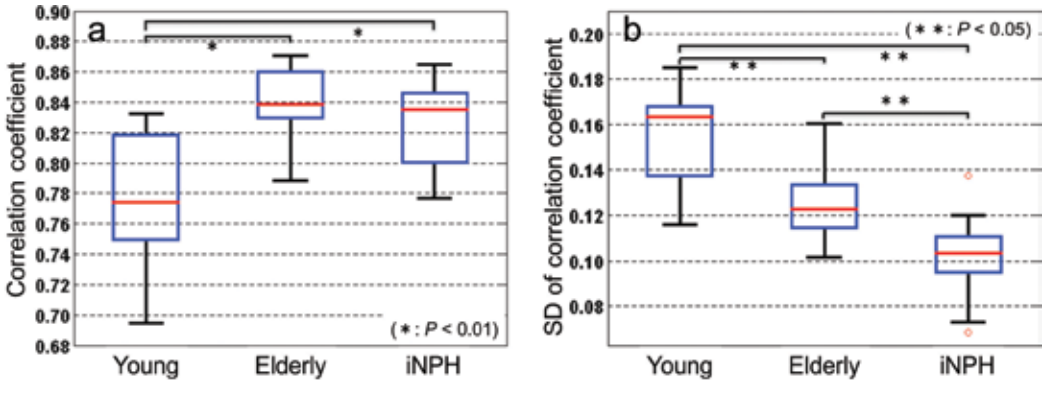

Figure 9. Boxplot of the mean correlation coefficient in the intracranial CSF space for the three subject groups is shown in (a) and the standard deviation (b).

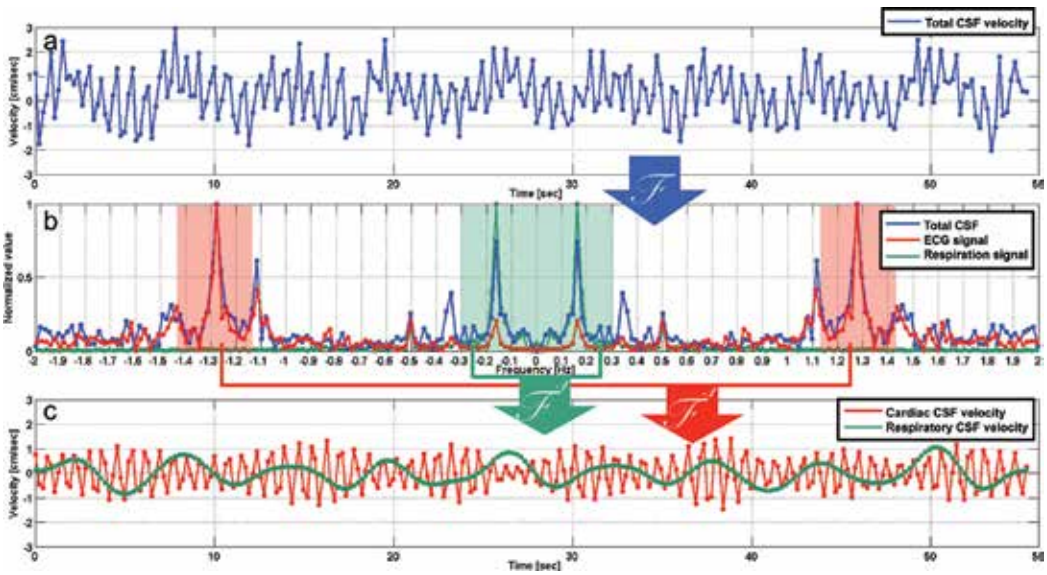

Figure 10. Cardiac- and respiratory-driven CSF velocities were separated from the total velocity by Fourier and inverse Fourier transformations.

of the lateral ventricle, and the pixel brightness was relatively high. In 6-, 10-, and 16-s respiratory cycles, the power ratios between the cardiac- and respiratory-driven components at the anterior cistern of the brainstem are compared in **Figure 12(a)**, while the ratios of quantitative analysis in 6-s respiration are exhibited in **Figure 12(b)**. Significant differences between the cardiac and respiratory energy were observed at all respiratory periods, while the power ratios at 6 s were significantly different in ROIs #1–3. **Table 2** summarizes the average and standard deviation of the cardiac and respiratory fractions for each respiratory cycle. Significant differences were obtained in the same ROIs at various respiratory cycles.

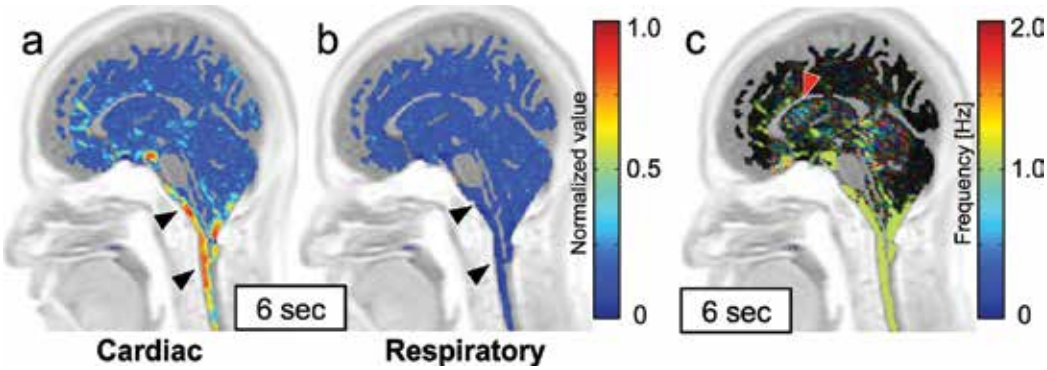

Figure 11. The cardiac (a) and respiratory (b) P-map in a 6-s respiratory period (≈0.167 Hz). The cardiac CSF energy was apparently high at the anterior cistern of the brainstem and spinal subarachnoid space shown by a black arrowhead. (c) An example of an F-map in a 6-s respiratory period. Brightness was changed based on the average of the maximum peaks of CSF power spectra in the CSF space. At the anterior part of lateral ventricle shown by a red arrowhead, this region had mixed various frequencies and relatively high velocities.

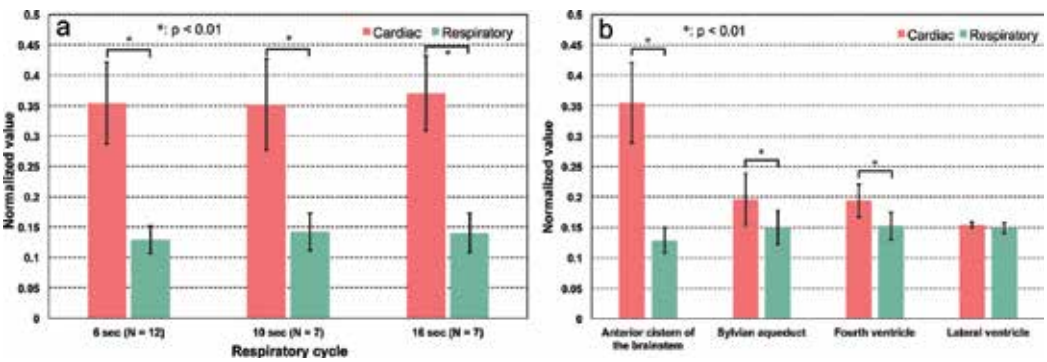

Figure 12. (a) Fractions of the cardiac and respiratory powers with the number of subjects (N) at ROI #1 depicted in **Figure 3**. (b) Fractions of the cardiac and respiratory CSF energies at various ROIs in a 6-s respiratory cycle.

	6 s		**10 s**		**16 s**	
	Cardiac	**Respiratory**	**Cardiac**	**Respiratory**	**Cardiac**	**Respiratory**
Anterior cistern of the brainstem	$0.355 \pm 0.065^{*}$	0.127 ± 0.021	$0.353 \pm 0.072^{*}$	0.141 ± 0.030	$0.370 \pm 0.061^{*}$	0.140 ± 0.032
Sylvian aqueduct	$0.196 \pm 0.043^{*}$	0.150 ± 0.028	$0.205 \pm 0.051^{*}$	0.159 ± 0.031	$0.208 \pm 0.052^{*}$	0.145 ± 0.025
Fourth ventricle	$0.194 \pm 0.027^{*}$	0.151 ± 0.023	$0.189 \pm 0.011^{*}$	0.154 ± 0.024	$0.192 \pm 0.014^{*}$	0.149 ± 0.018
Lateral ventricle	0.154 ± 0.005	0.148 ± 0.009	0.152 ± 0.006	0.151 ± 0.007	0.154 ± 0.008	0.147 ± 0.007

$^{*}p < 0.01$
Significant differences were recognized between the cardiac and respiratory components at each respiratory cycle ($p < 0.01$).

Table 2. The energy fractions (average ± SD) at the ROIs in three different respiratory cycles.

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Figure 13(a) indicates the typical cardiac pressure gradient image at the maximum positive pressure gradient, while **Figure 13(b)** is that at the negative. **Figure 13(c)** and **(d)** is the same but for the respiratory pressure gradient. Moreover, the results of the quantitative analysis of the cardiac and respiratory pressure gradients were depicted in **Figure 13(e)**. At all the ROIs, significant differences were recognized between the cardiac and respiratory pressure gradients.

The peak-to-peak velocity of the cardiac and respiratory components and the fraction of those were assessed, as shown in **Figure 14**. **Figure 14(a)** presents a significantly higher velocity of the cardiac-driven CSF motion at #1 and #2 than that of the respiratory-driven motion ($p < 0.01$). The fraction in **Figure 14(b)** exhibited the significant differences in all ROIs ($p < 0.01$).

The correlation mapping technique applied to the cardiac- and respiratory-driven CSF motions in a healthy volunteer, as depicted in **Figure 15(a)**, demonstrated a difference in the propagation

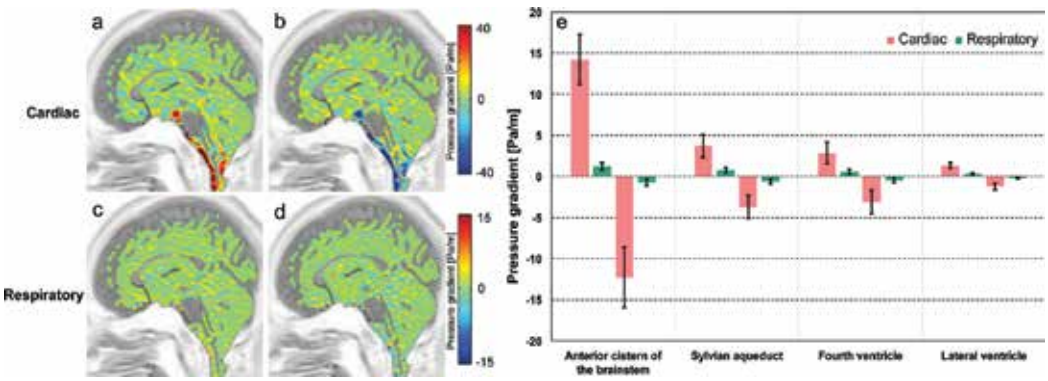

Figure 13. Typical examples of pressure gradient distributions calculated by the separated cardiac- and respiratory-driven CSF velocity. (a) and (b) are the maximum positive and negative gradients of the cardiac, while (c) and (d) are those of the respiratory. In the anterior cistern of the brainstem, the cardiac component was obviously high compared to the respiratory component. (e) Quantitative analysis of the pressure gradients at the ROIs. The upward bars present the positive pressure gradients, while the downward show the negative.

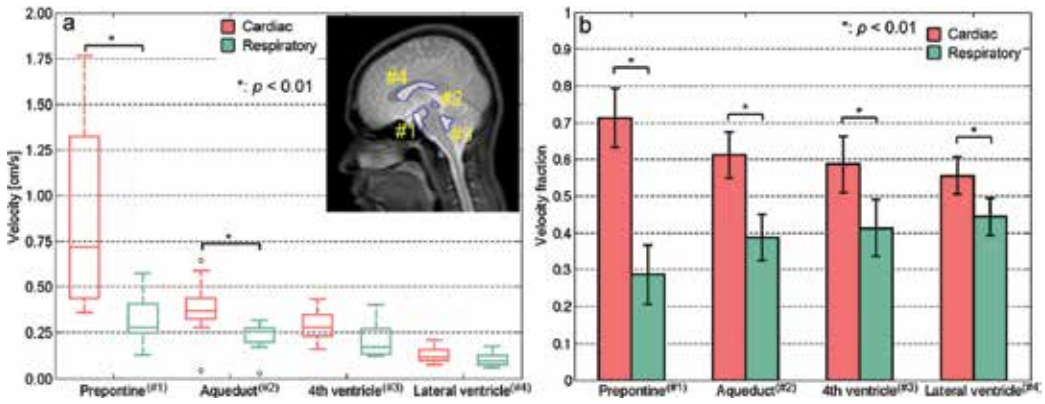

Figure 14. Cardiac- and respiratory-driven CSF velocities were compared at ROIs, the prepontine (#1), aqueduct (#2), fourth ventricle (#3), and lateral ventricle (#4) indicated on T2 images, as shown in (a). The fraction of the cardiac- and respiratory-driven CSF velocities is shown in (b).

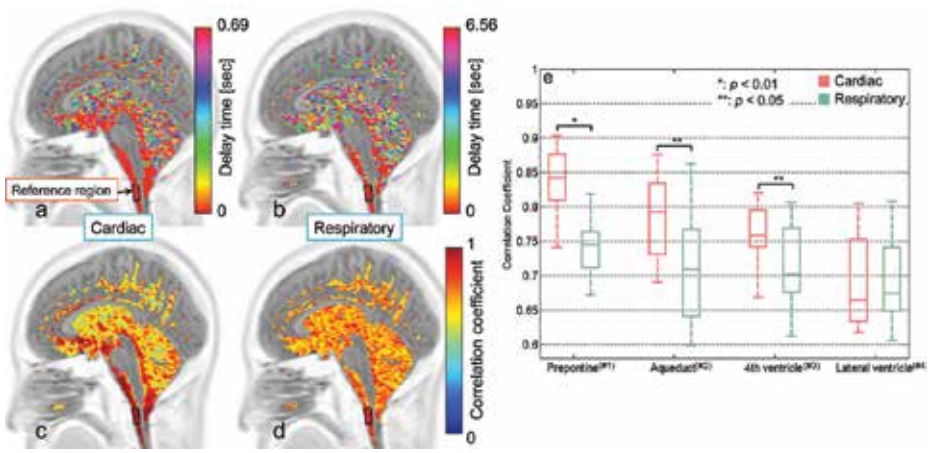

Figure 15. Delay time (a and b) and maximum correlation (c and d) maps of the cardiac- and respiratory-driven CSF velocities for a healthy volunteer; (e) quantitative results of maximum correlation in the ROIs in **Figure 14**. Propagation differences between the cardiac and respiratory were observed.

properties between those motions in intracranial space. The cardiac delay time was short around the brainstem and gradually prolonged with the distance from the reference. In addition, the maximum correlation map indicated a high correlation near the brainstem and low in the midbrain part. The respiratory-driven motion showed scattered delay time distribution and consistently high correlation distribution in contrast to those of the respiratory-driven. The maximum correlation is quantified in **Figure 15(e)**. There are significant cardiac and respiratory differences in #1 ($p < 0.01$), #2 ($p < 0.05$), and #3 ($p < 0.05$).

The CSF displacement, the fraction between the cardiac and respiratory components calculated by the velocity integration, and the displacement modified in accordance with the energy leaking out from the selected band in frequency domain are shown in **Figure 16**. The

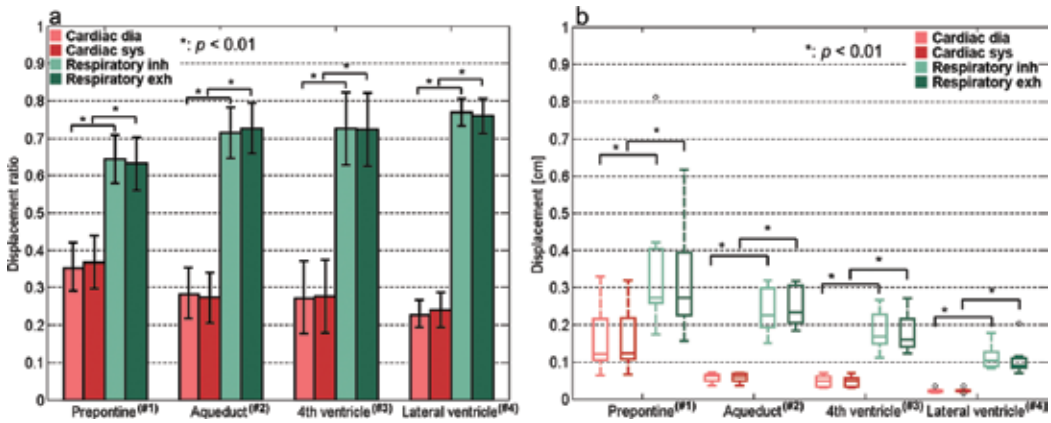

Figure 16. Fractions of the cardiac- and respiratory-driven CSF displacements (a) and the value of displacements modified for the velocity energy leaking out from the selected bandwidth in the frequency domain (b), in the same ROIs as **Figure 14**.

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displacement fractions, as well as the displacement values with the energy leak compensation, were significantly larger in the respiratory- than in the cardiac-driven motion in all the ROIs ($p < 0.01$).

4. Discussion

This chapter described techniques to visualize and characterize CSF motion in intracranial space based on PC velocity imaging. They provide quantitative information on CSF motion, which would be useful for clinical diagnosis.

The 4D-VM technique visualized and characterized various quantities of the cardiac-driven CSF motion. The curl images showed the disturbance of motion, and the pressure gradient represented the pressure propagation that may relate to the driving force. The delay time and the maximum correlation exhibited differences in the cardiac-driven CSF motion among the young, healthy, elderly, healthy, and iNPH patient groups. The presence of delay and correlation variations indicates the presence of compliance in the CSF space and brain parenchyma, as CSF is an uncompressible fluid. Brain compliance decreases with age and iNPH status [26, 27]. The velocity, curl, pressure gradient, delay time, and correlation images may reflect hydrocephalus. The limitations of the cardiac-gated PC imaging are the long acquisition duration and the lack of the information on the respiratory-driven motion.

The asynchronous PC technique separated the cardiac- and respiratory-driven CSF motions. The P- and F-maps indicated that the cardiac component is predominant in the anterior cistern of the brainstem. There are major arteries, such as the basilar artery, which may cause the strong cardiac-driven CSF motion around this tissue region. In addition, the cardiac pulsation period is remarkably shorter than that of respiratory pulsation. The instantaneous and strong cardiac pulsation induces a large pressure gradient resulting in the predominant CSF motion in comparison with the cardiac-driven motion. Moreover, velocity analysis as well as correlation mapping exhibited that the cardiac component was significantly larger than the respiratory component. Thus, the difference between the cardiac and respiratory driving forces appeared in power, frequency, delay time and correlation mapping, and displacement analysis based on asynchronous PC imaging. On the other hand, the respiratory-driven displacement was larger than that of the cardiac because the blood volume change induced by respiration is known to be larger than that induced by cardiac pulsation [6]. This suggests that a high velocity of CSF does not necessarily mean large displacement.

The asynchronous PC technique has several limitations, such as its relatively low temporal resolution and ignorance of the bulk flow. The temporal resolution achieved in the present work was 217 ms corresponding to 4.61 frames/s. Acceleration techniques, such as compressed sensing with sparse sampling, may be needed for higher frame rates and thus accurate evaluation of the CSF motion. The bulk flow, whose velocity may be in the order of molecular diffusion, must be investigated to understand the mass transfer or washout mechanisms in the brain.

5. Conclusion

The usefulness of the MR techniques, such as 4D-VM, correlation mapping, power and frequency mapping, and displacement analysis based on cardiac-gated and asynchronous PC imaging, were described.

Acknowledgements

The authors thank Prof. Yutaka Imai and Dr. Koichi Oshio for their valuable discussions. They also thank Mr. Tomohiko Horie and Mr. Nao Kajihara for their assistance in MR imaging.

Conflict of interest

The authors declare they have no conflicts of interest.

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Chapter 3

Craniocervical Junction Syndrome: Anatomy of the Craniocervical and Atlantoaxial Junctions and the Effect of Misalignment on Cerebrospinal Fluid Flow

Scott Rosa, John W. Baird, David Harshfield and Mahan Chehrenama

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72890

Abstract

The craniocervical junction (CCJ) is comprised of the inferior surface of the skull, the atlas and axis, as well as muscles and connective tissues that attach the skull to the cervical spine. The CCJ encloses the central nervous system (CNS), encephalic vasculature and the cerebrospinal fluid (CSF) system. The CCJ spans the brainstem to the spinal cord, including the vascular system as well as connecting the cerebrospinal fluid (CSF) cisterns within the skull to the CSF channels in the spinal canal. Malformation and misalignment of the craniocervical junction can cause a constellation of cerebral and other neurological signs and symptoms collectively called craniocervical syndrome (CCS). The signs and symptoms of craniocervical junction syndrome may be due to mechanical strain causing deformation of dura mater, vasculature and other structures of the cranial vault resulting in irritation of and dysfunction of affected tissues. Deformation of the CCJ may also obstruct blood and CSF flow. Chronic ischemia, edema and hydrocephalus can cause degenerative cascades that can in turn lead to neurodegenerative diseases.

Keywords: craniocervical junction, hydrocephalus, ligament disruption, CFS flow, CSF obstruction, cerebellar tonsillar ectopia, brain stem compression, IGAT, image guided atlas treatment

1. Anatomy of the craniocervical junction

The cervical spine is made up of seven vertebrae divided into upper and lower sections. The upper cervical spine includes the first two vertebrae, classically named atlas (C1) and axis (C2). The CCJ links the skull to the upper cervical spine and therefore the foramen magnum

to the spinal canal. The atlas is essentially a ring of bone formed by two arches that are flanked and joined by the lateral masses, which contain the superior and inferior facets [1].

The transverse processes of the atlas are attached to the lateral masses and contain the intertransverse foramina. The intertransverse foramina of the cervical spine form a flexible protective tunnel for the passage of the vertebral arteries. The alignment of occiput (C0) with the atlas and axis is crucial to the integrity and functional architecture of the spinal cord and mid brain structures [2]. Like the entire spine, this connection is primarily ligamentous and membranous in nature. The atlantoaxial joint (C1–2) is arguably the most unique and complex of all spinal intersegmental relationships. The relative horizontal to biconvex orientation of the opposing weight-bearing facets allows excellent rotation at the expense of osseous stability [3]. The transverse band of the cruciate ligament arises from tubercles on the atlas lateral masses and stretches across and behind the dens of C2 holding the odontoid process (dens) against the anterior arch preventing migration of the dens into the spinal canal [4–6].

The alar ligaments are much larger and stronger than the apical or accessory ligaments. Damage to the alar ligaments can cause joint instability and excess motion [7]. Excess motion can lead to kinking or compression of the vertebral arteries and irritation of nociceptor and mechanoreceptors, which may play a role in symptoms such as headache, neck pain and dizziness associated with head/neck trauma and whiplash-type injuries (**Figure 1**).

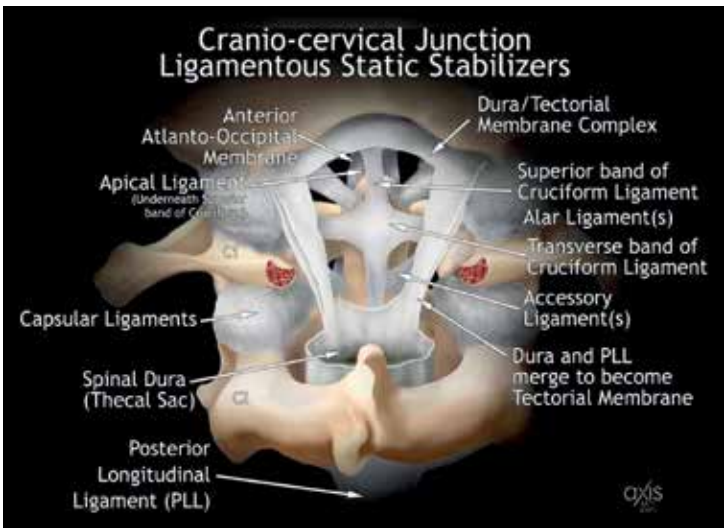

Figure 1. Coronal illustration of the ligamentous stabilizers of the Cranio-cervical junction.

The anterior and posterior spinal longitudinal ligaments (ALL and PLL) are major stabilizers of the anterior and middle columns of the entire spinal axis [8]. The posterior longitudinal ligament transcends into what becomes the anterior dura-mater/tectorial "membrane" complex cephalad to the mid C2 vertebral body (the longitudinal collagenous architecture of the tectorial "membrane" is indistinguishable from the posterior longitudinal "ligament"). The ALL and PLL are two "paired" ligaments known as the suboccipital stabilizers to flexion and extension stress [9, 10]. The capsular ligaments stabilize the facet joints by limiting flexion and rotation (**Figure 2**) [11].

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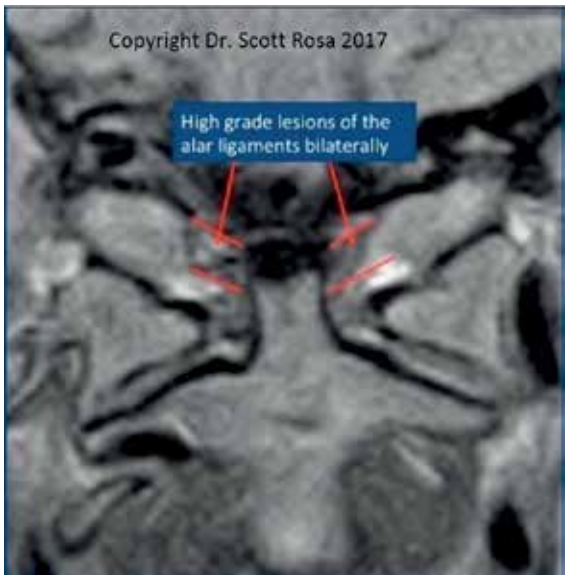

Figure 2. Disruption of the alar ligaments.

The tectorial membrane is a continuation of the posterior longitudinal ligament and ultimately coalesces with the periosteum lining along the anterior margin of the foramen magnum at the basion [6, 12, 13]. The Tectorial Membrane (TM) plays a substantial role in stabilizing the cranio-cervical junction, especially by limiting flexion. During head/neck trauma, hyperextension/hyperflexion and translation take place at the cranio-cervical junction. Hyperflexion alone or combined with anterior translation is the presumed mechanism for injury/damage to the TM (**Figures 3** and **4**) [14].

Grading of ligament disruption is as follows:

1. Partial thinning involving less than 1/3rd the width of the TM (grade I lesion) can represent a normal variant,
2. Lesions involving up to 2/3rd's of the width (grade II) may be seen as a consequence of head/neck trauma and or repetitive micro-stress.
3. Complete absence of or disruption of greater than 2/3rds of the membrane (grade III lesion), accompanied by a normal or partially ruptured dura mater, has not been described in the normal patient population [15].

Weakening and disruption of the key stabilizers of the CCJ can lead to a head forward posture resulting in loss or reversal of the cervical lordosis. This straightening effectively lengthens the spinal canal. The dentate ligaments stabilize the position of the spinal cord in the center of the spinal canal. The spinal cord subsequently can become tethered to each spinal segment by way of the dentate ligaments, and such loss of the cervical lordosis may create traction on the spinal cord resulting in a caudal downward pulling of the brain and cranial elements (brainstem/cerebellar tonsils) downward into the foramen magnum [16, 17]. This can result in

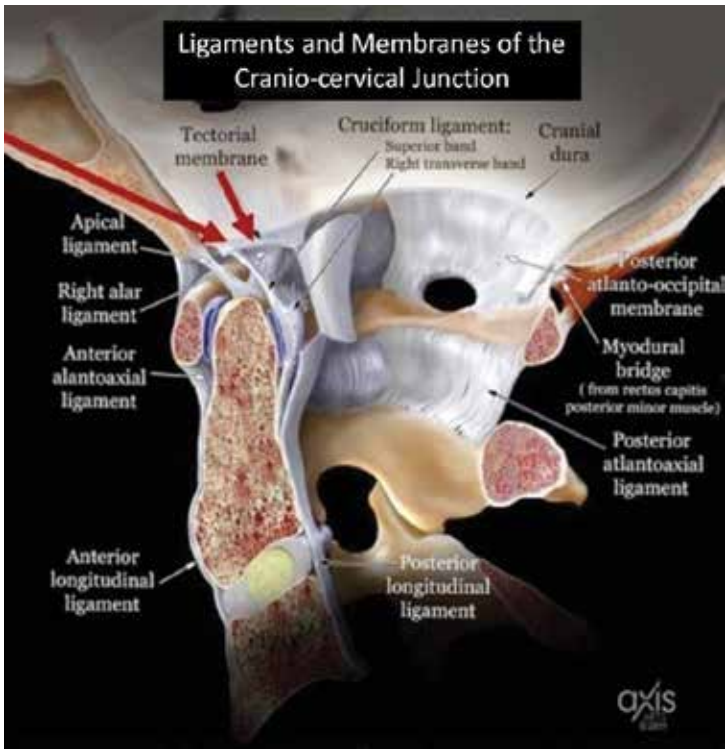

Figure 3. Sagittal illustration of the ligamentous stabilizers of the Cranio-cervical junction.

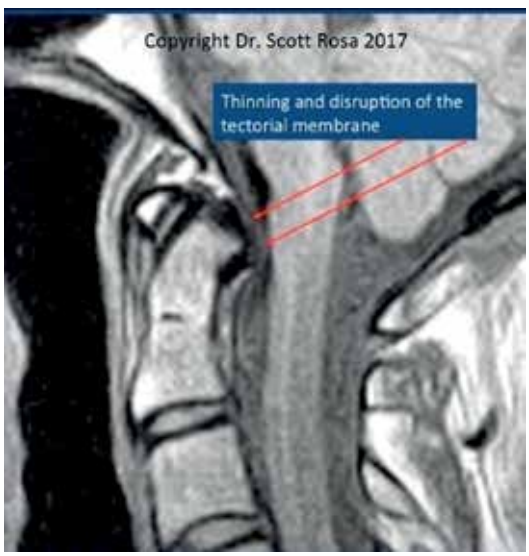

Figure 4. Disruption of the tectorial membrane.

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an acquired cerebellar tonsillar ectopia, which can interfere with the cerebral spinal fluid flow of CSF, resulting in a disequilibration of arterial and venous flow while degrading the nutritive, restorative and support function of the CSF for the central nervous system (**Figure 5**) [18].

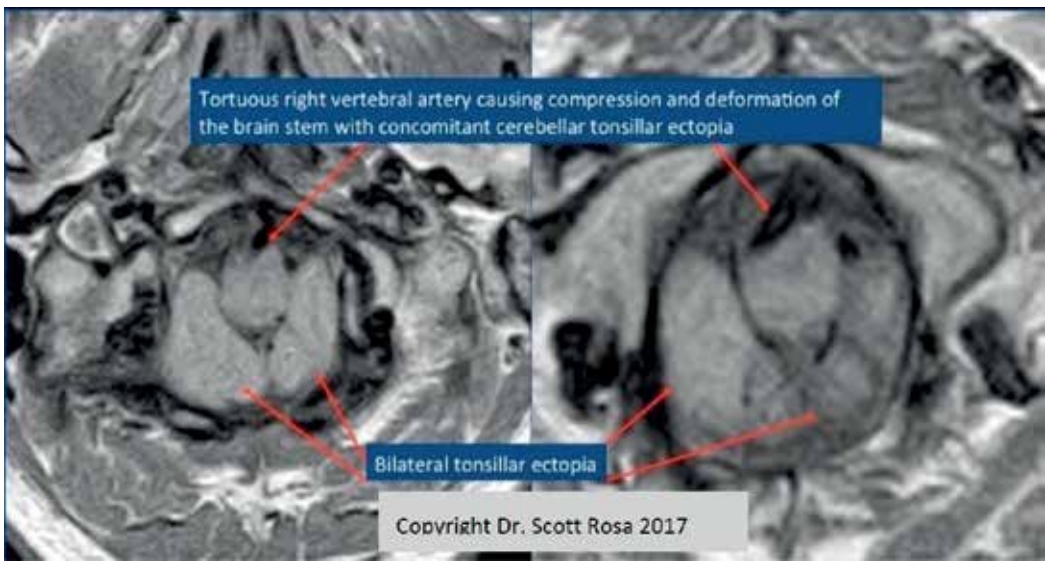

Figure 5. Brain stem compressed by the right vertebral artery. Low cerebellar tonsils.

Rotary misalignments of C1–2 can impair the normal CSF flow as well as contributing to an insufficiency of blood flow of the vertebro-basillar system (**Figure 6**).

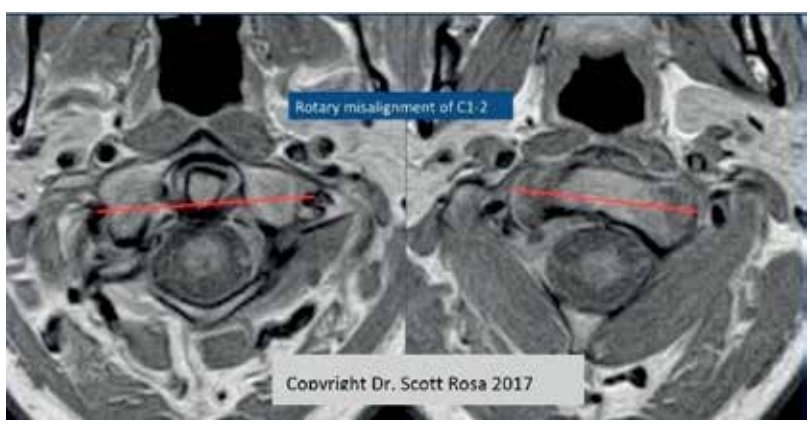

Figure 6. Rotary misalignment of atlas (C1) and axis (C2).

A tortuous vertebral artery may be visible on MRI imaging. Pulsatile compression of the brain stem by the vertebral artery is associated with cerebellar dysfunction, hydrocephalus, ischemic

stroke, transient or permanent motor deficits, central sleep apnea, trigeminal neuralgia, as well as brain stem compression syndrome [19–21].

FONAR upright weight bearing MRI has been shown to be most sensitive in detecting cerebellar tonsillar ectopia since weight- bearing posture presents the cerebellar tonsils further distended into the foramen magnum [18]. Visualization of misalignment of the craniocervical junction and its effects on the nervous system is also demonstrated when images are acquired under the effects of gravity. Imaging of the sagittal, coronal and axial planes ensure a fulsome evaluation of the adequacy of the foramen magnum and provides good sensitivity in the evaluation of the cerebellar tonsils (**Figures 7–10**).

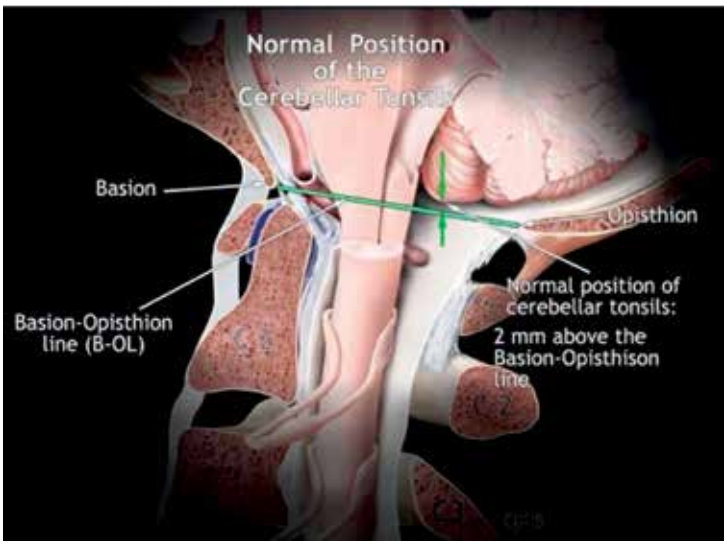

Figure 7. Normal position of cerebellar tonsils.

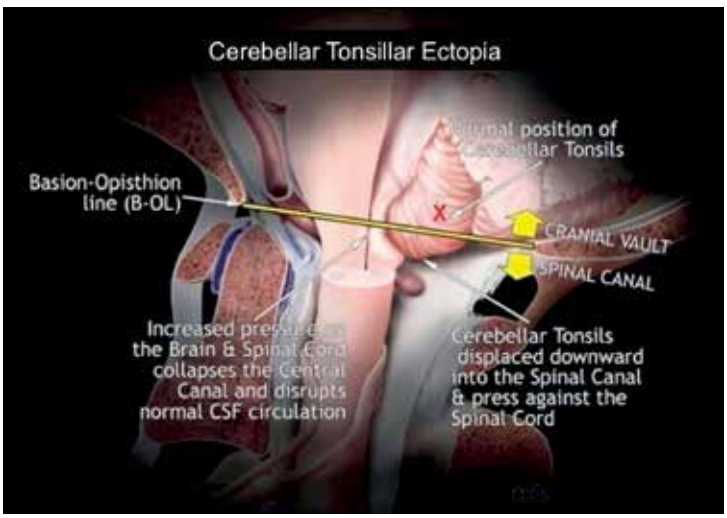

Figure 8. Cerebellar tonsillar ectopia.

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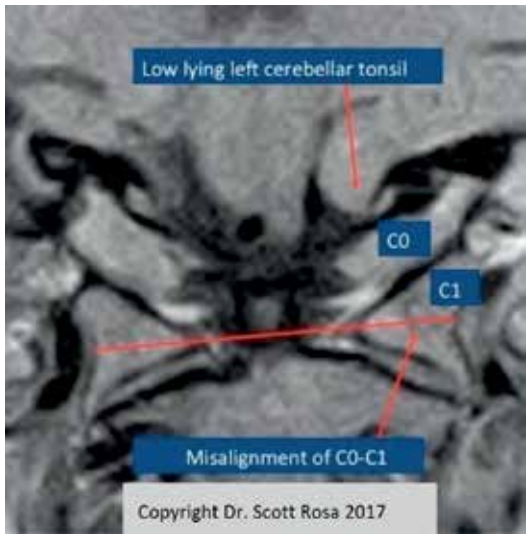

Figure 9. Coronal view demonstrating misalignment of C0-C1 with left cerebellar tonsillar ectopia.

Figure 10. Bilateral cerebellar tonsillar ectopia demonstrated on the coronal view (left) and on the axial view (right).

2. CSF flow

In 1891, Chiari discovered anomalies involving the cerebellar tonsils while performing postmortem examinations on children and adolescents with cerebral hydrocephalus. He recognized that the size of these structural defects in the brain was not related to the severity of the hydrocephalus [18].

The classic definition of Chiari malformation is herniation of the cerebellar tonsils 3 to 5 mm below the foramen magnum. This excess tissue in the upper cervical spinal canal creates pressure and disrupts the flow of cerebrospinal fluid (CSF). Blocked spinal fluid can cause hydrocephalus or, as is more common in Chiari malformation, a fluid-filled cyst known as a syrinx [22].

Spinal integrity may be restored through reduction of misalignments at the cranio-cervical junction. Image Guided Atlas Treatment (IGAT tm) has been shown to be effective at restoring CSF flow reducing and reversing the neurodegenerative cascade [23].

Image-Guided Atlas Treatment (IGAT) utilizes dynamic upright MRI imaging sequences in order to permit proper visualization of the CCJ misalignments (**Figure 11**).

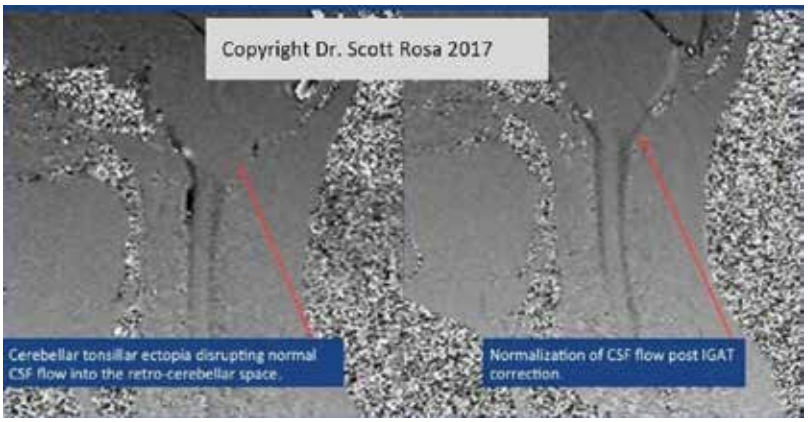

Figure 11. Disruption of CSF flow (left) with restoration of normal flow post IGAT (right) on phase contrast cine CSF flow MR.

Cerebrospinal fluid (when unencumbered) contains low-molecular weight chelating agents that remove metal atoms from the interstitial spaces of the brain and spinal cord, as well as from neurons and glial cell membranes. Abnormal iron deposition is a consequence of the cascade of malevalence associated with cerebellar ectopia induced CSF stasis [24]. What is equally surprising, if not more so, is the fact that ferromagnetic mineral magnetite (Fe3 O4) crystals are formed biochemically as a manifestation of normal brain tissue metabolism. Parkinson's and Alzheimer's diseases may by induced by toxic build-up of heavy metals-within the basal ganglia in the case of Parkinson's, and in the cortical and sub-cortical regions of the brain in the case of Alzheimer's disease (**Figure 12**).

With the cascade of CSF pathophysiology induced by cerebellar tonsilar ectopia, there is compromise of the total encephalic venous outflow due to obstruction of the venous system that cannot be adequately shunted from the cranial vault. Portions of the superficial venous system draining the frontal, parietal, temporal, and occipital lobes are also drained by direct connections into the transverse sinuses and the middle cerebral veins. The inability to redistribute or disperse the obstructed superficial venous outflow results in intracerebral venocongestion, leading to loss of intracerebral compliance thereby decreasing intracerebral blood flow.

Review of available data provides a reasonable model of cerebral venous outflow that, when used in conjunction with our understanding of arterial blood supply and CSF dynamics, may explain much of the pathophysiology of hydrocephalus [25].

Simultaneous obstruction of both the "principal" and "collateral venous outflow" tracts (as an indirect result of cerebellar tonsillar ectopia) can lead to elevated venous pressure and

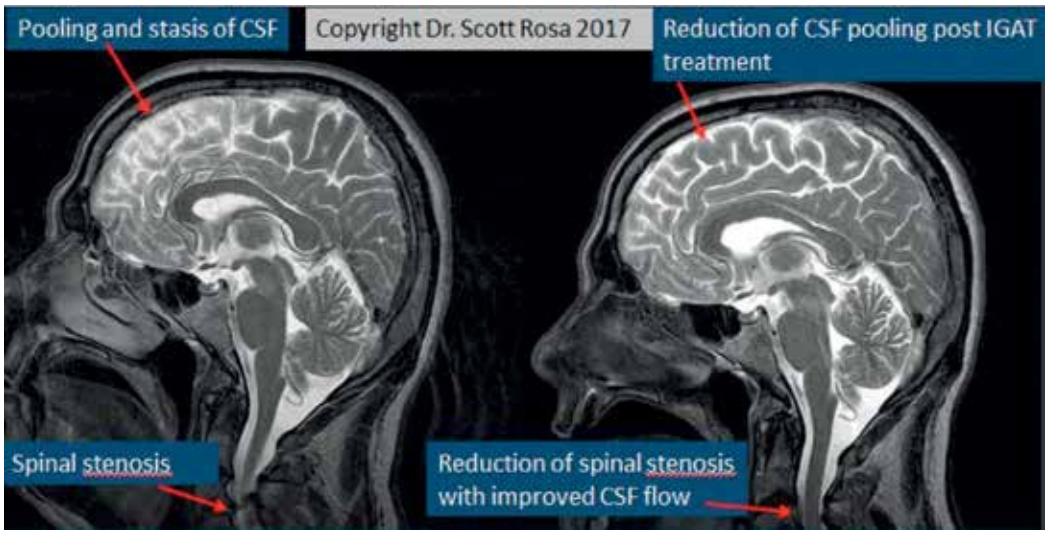

Figure 12. Obstructed effusion of CSF from the cranium may result in pooling and stasis (left). Correction of spinal misalignment results in improved CFS flow (right).

eventually to insufficiency of cerebral blood flow (CBF). With increased intracranial pressure (and decreasing intracranial compliance), ventricular enlargement may occur due to atrophy of the periventricular white matter.

Cerebrospinal fluid shunting (surgically) results in an initial increase in CBF as the essential therapeutic effect in treating patients with hydrocephalus, but ultimately CSF shunting precipitates venocongestive brain edema, which helps explain the reduced ventricular size along with the known side effects of shunting [26].

Upright Ciné MRI of the cranio-cervical junction demonstrates CSF flow dynamics. MRI examination of the brain reveals subtle structural defects in addition to any obvious tonsillar ectopia.

Subtle deformities within the posterior fossa, with or without frank herniation, can be more problematic in their effect on brain function than a large but simple ectopia that leaves room for normal fluid flow. This explains why short, thick cerebellar tonsils that barely plug the foramen magnum can cause a serious impediment, while a longer herniation that is thin or peg-shaped sometimes may cause few problems [27]. The encroachment of the cerebellar vermis and tonsils on the foramen magnum disturbs the CSF flow patterns, thereby precipitating headaches and other neurological symptoms [25–32].

3. Radiological features

Imaging studies of the cranio-cervical junction, particularly standard MRI, lacks sensitivity when viewing the CCJ ligaments for signs of sub-failure. X-ray based imaging (conventional radiographs, fluoroscopy and CT), do not show ligament tears, particularly when chronic scarring replaces the "thickness" of the normal cable-like arrangement of collagen in healthy ligaments [33, 34]. Intraligamentous heme is released when ligaments are torn, creating a

susceptibility artifact, particularly on T2 weighted images, making the torn ligament appear "normal" (uniform, hypointense, "dark" signal with uniform thickness) [35]. With proper MRI sequences, such as "Proton Density" thin section data sets, the "gray" intermediate signal indicative of ligamentous disruption can be contrasted by a background of adjacent "brighter" CSF (versus intermediate signal with T1 weighting) [36].

Standard T1 W and T2 W CCJ MRI protocols with 5- to 7-mm-thick slices are insufficient to demonstrate such membrane/ligament lesions [37]. Sections 2–3 mm thick give adequate spatial resolution with an adequate signal-to-noise ratio. The low membrane/ligament signal afforded by proton density (PD)-weighted images provide better delineation from both CSF and adjacent soft tissues compared to the standard T1- and T2-weighted sequences that typically comprise standard cervical MRI studies [38].

On T1-weighted images, ligaments are not as well defined because a damaged ligament and the surrounding edema/inflammation and adjacent CSF will all be 'gray', or intermediate in T1 signal [15]. However, with the PD sequence (especially with fat suppression) the edema/inflammation and CSF become hyperintense (increased in PD signal) while depicting intact ligaments as relatively hypointense (lower) signal. The reason PD-weighted images are not routinely used to replace the standard T1-weighted images (on current C-spine protocols) is that PD can "miss" medullary space lesions [39].

In hyperflexion trauma, all posterior cervical ligaments and membranes are subjected to strain forces. When the atlanto-occipital membrane is stretched beyond its elastic limit, these forces are transmitted to the adjacent dura mater. The rupture of the latter indicates a sprained/injured membrane.

4. Kinematic imaging of the craniocervical junction

The complex nature of the structure and function of the craniocervical junction makes it especially vulnerable to injury and deformation. Forces acting upon the head and cervical spine as occurs in head/neck trauma, may occur in complex patterns [40]. Accordingly, it is important to ensure that complex injuries are properly evaluated and are not overlooked as complex injury scenarios are plausible when trauma occurs to the craniocervical junction [41].

Acknowledgements

The authors would like to acknowledge Dr. Michael Flanagan's numerous contributions to the literature and his seminal writings on the anatomy of the craniocervical junction and the role of cerebrospinal fluid in brain function and health. https://uprightdoctor.wordpress.com/about-dr-michael-flanaga/

Special thanks to Ron Tribell and Axis Medical Illustrations for the illustrations at **Figures 1**, **3**, **7** and **8**.

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Section 3

Clinical and Cognitive Features of NPH

Chapter 4

Clinical and Cognitive Features of Idiopathic Normal Pressure Hydrocephalus

Elena Sinforiani, Claudio Pacchetti, Marta Picascia, Nicolò Gabriele Pozzi, Massimiliano Todisco and Paolo Vitali

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73273

Abstract

Introduction: Idiopathic normal pressure hydrocephalus (iNPH) is characterized by dilated cerebral ventricles with progressive impaired gait, cognition, and urinary control. Firstly described in 1965 by Hakim and Adam, it remains largely under-diagnosed. The diagnosis is based on clinical and imaging (CT or MRI) investigations; a timely diagnosis and cerebrospinal fluid (CSF) shunt surgery has reported to be beneficial in 60 up to 80% of the cases.

Body: The severity of motor and cognitive disturbances varies widely and it can be difficult to distinguish iNPH from other neurodegenerative disorders. The cognitive and behavioral disturbances have been commonly described as "fronto-subcortical dysfunction". However, this definition is reductive not encompassing the entire cognitive spectrum of iNPH deficits. In our sample we found an impairment in respect to healthy controls in all the neuropsychological tests, but verbal memory. We could also find a positive correlation between the severity of cognition deficit and disease progression, suggesting a common pathological mechanism.

Conclusions: iNPH can be reliably diagnosed with an organized approach. Neurologists play an essential role in the care of patients and a multidisciplinary team can improve this process. An early shunt surgery might contain the progression of the disturbances and also possibly prevent their development.

Keywords: hydrocephalus, neurodegenerative diseases, cognition, aging and dementia, neurogeriatric

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) was described for the first time in 1965 by Hakim and Adam as ventricular dilation accompanied by a progressive triad of a gait disturbance, "dementia" and incontinence. Usually gait and balance disorders appear early and are the most impressive symptoms, cognitive decline and incontinence generally appear later as the disease progresses [1].

The symptoms presented usually appear as:

- Gait disturbances as apraxia or that are commonly seen in parkinsonism (bradykinetic, magnetic and shuffling gait).
- Urinary incontinence: urinary frequency, urgency, or frank incontinence.
- Dementia: executive dysfunction, psychomotor slowing, prominent memory loss, visuospatial difficulties, decreased attention, apathy.

The gait disturbance is typically the earliest feature noted and is considered to be the most responsive to treatment. The primary feature is thought to resemble an apraxia of gait or a "lower body parkinsonism". True weakness or ataxia is typically not observed. The severity of gait disorders range from mild to the wheelchair.

The urinary symptoms of NPH can present as urinary frequency, urgency, or incontinence. While incontinence can result from gait disturbance and dementia, in a study by Sakakibara and colleagues [2] 95% of patients had urodynamic parameters consistent with detrusor overactivity.

The cognitive and behavioral disturbances accompanying iNPH have been commonly described as "fronto-subcortical dysfunction".

However, this definition is reductive not encompassing the entire cognitive spectrum of iNPH deficits. We will deal with this topic more in detail later on.

The incidence of iNPH is between 2 and 6% among people affected by any dementia condition; its occurrence is probably underestimated. Brean and Eide [3] reported a prevalence of 21.9/100,000 and an incidence of 5.5/100,000 in a Norwegian population, which are probably minimum estimates according to the authors.

A more recent epidemiological study [4] confirms this impression: the prevalence of probable iNPH has been reported to be 0.2% in subjects aged 70–79 years and 5.9% in those aged 80 years and older, respectively, without difference between men and women. Moreover, as the authors wrote: "the number of subjects with iNPH is probably much higher than the number of persons currently treated", and since the prevalence increases with increasing age they estimate approximately that 2 million persons in Europe and 700,000 in the United States may have iNPH.

A high incidence was also reported by Iseki et al. [5] in a 10-year follow-up study of a population of 70 year olds from a rural Japanese community. A recent systematic epidemiological review [6] confirmed that this pathology is under-diagnosed.

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The need for guidelines and operating criteria for the diagnosis and management of this condition was firstly implemented by the Japanese Society of Normal Pressure Hydrocephalus in 2004; as the paper however was available only in Japanese, in 2005 Marmarou et al. [7] published English language guidelines designed to be "acceptable in the United States and abroad". Then, as there were some differences between the two guidelines, International and Japanese, in 2008 Ishikawa et al. [8] proposed an English and up to date version of the previous Japanese guidelines in order to make them known worldwide.

Finally, in 2012, given the significant increase in basic and clinical research on iNPH and the availability of more high level evidence, Mori et al. [9] published a revision of the English language version of the Japanese guidelines.

More recently, Williams and Relkin [1] have published detailed indications on the diagnosis and management of iNPH; on the basis of an extremely clinical approach, the authors stress the concept that the starting point should be a comprehensive history and neurological examination, review of neuroimaging studies, and evaluation of the differential diagnosis. Moreover, the article reports a comparison between the International and Japanese Guidelines, where the former are more exhaustive regarding the clinical features.

2. Imaging studies

In most cases of new onset of neurologic symptoms, a computerized tomography (CT) scan of the brain is initially obtained. Although magnetic resonance imaging (MRI) is more specific than CT in iNPH, a normal CT scan can exclude the diagnosis. As shown in **Figure 1** MRI findings in iNPH include the following:

- ventricular enlargement out of proportion to sulcal atrophy, with typical rounding of frontal horns
- prominent periventricular hyperintensity consistent with transependymal flow of CSF and/or leukoaraiosis
- aqueduct perviety (or slight enlargement) to exclude congenital stenosis. A more specific sign, prominent flow void in the aqueduct, the so-called hyperdynamic aqueduct or jet sign, requires spine-echo sequences, currently dismissed in routine MRI, replaced by the faster turbo-spin-echo sequences, (Today, a confirmation of the hyperdynamic aqueduct should be obtained by measuring aqueduct cerebral spinal flow (CSF) stroke volume by phase-contrast MRI [10]
- thinning and elevation of corpus callosum on the median sagittal slice, and acute callosal angle in the coronal slice passing through the posterior commissure [11].

A narrow CSF space at the high convexity/midline areas relative to Sylvian fissure size was recently shown to correlate with a diagnosis of probable or definite iNPH. This specific sign, called "Disproportionally enlarged Subarachnoid spaces Hydrocephalus" (DESH) [12] has been found the most sensitive to the ventricular shunting. To establish a diagnosis of NPH, an

MRI or CT must show an Evans index of at least 0.3 [13]. In addition, to exclude hydrocephalus ex vacuo, one or more of the following must also be present:

- disproportionally enlarged subarachnoid spaces hydrocephalus (DESH)
- acute callosal angle
- hyperdynamic aqueduct.
- Pathophysiology

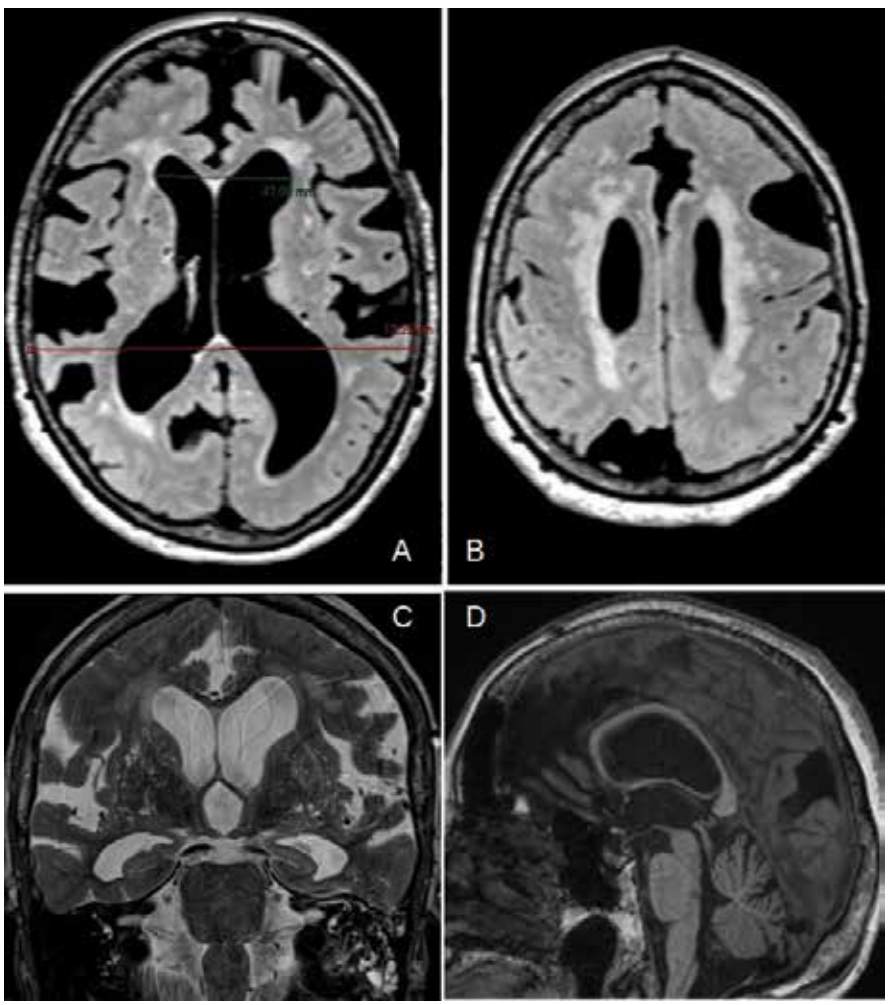

Figure 1. A: Axial FLAIR shows periventricular white matter changes, ventricles dilatation in both frontal and occipital horns, Evan's index >0.30 B: Axial FLAIR at upper level shows global sulcal thinning and focal sulcal dilatation C coronal T2 shows acute callosal angle and disproportionally enlarged subarachnoidal spaces hydrocephalus (DESH) D sagittal T1 shows callosal bulging and mild aqueduct enlargement.

http://dx.doi.org/10.5772/intechopen.73273

The pathophysiology of iNPH is still not completely understood. iNPH differs from other causes of adult hydrocephalus, in which pathological changes alter the pressure of the cerebrospinal fluid (CSF), but it is also related to alterations of the CSF dynamicity [14].

The CSF space is a dynamic system, which constantly adapts its pressure to keep it constant. It responds to changes in CSF formation or reabsorption rates, arterial and venous flow, compliance of the intracranial structures and fluctuations in intracranial pressure (ICP). This process is essential for ensure the correct functioning of the brain. Indeed, the brain is enclosed in a fixed structure and any volume increase needs to be matched by a decrease to avoid changes of the intracranial pressure and consequential functional abnormalities.

The volume of blood entering the brain varies with the cardiac cycle, being present a net intracranial inflow of blood during systole and a net outflow during diastole. Arterial supply to the brain is pulsatile while venous flow is not, and this mismatch generates transient rises in CSF pressure. The system compensates for this in two different ways. First, the blood vessels can smooth the arterial blood influx modulating their compliance. Second, the CSF flows through the cerebral aqueduct in response to pulsatile blood flow, thus maintaining intracranial pressure stable. When these processes are altered, compensatory strategies are applied. However, the compensatory mechanisms that keep the CSF pressure constant may also produce other pathological alteration [14].

In iNPH, the compliance of the system is reduced, especially in the vessel of the superior sagittal sinus [15, 16]. This lack of arterial compliance is initially countered by increased pulsatile CSF flow through the aqueduct, but as the amplitude of arterial pulsatility increases, the blood flow in systole induces large ICP pulsations, determining the 'water hammer' effect. These exaggerated pulsations cause venous damage in the periventricular region and displace the brain toward the skull [17], thus determining the development of the hydrocephalus. Indeed, hydrocephalus occurs as a result of enlarging ventricles at the expense of a reduced subarachnoid space. This is secondary to increasing pressure within the ventricles directed toward the subarachnoid space, namely as increase of the transmantle pressure (i.e., the pressure gradient between the ventricles and the subarachnoid space) [17].

This pressure gradient also explains why, although there is increased intraventricular pressure, the measured opening pressure during a lumbar puncture is within normal limits. It also implies that 'normal pressure' in NPH is somewhat of a misnomer [14].

It is still unclear what triggers the initial reduction in arterial compliance. Deep white matter ischaemia surrounding arterioles may explain the loss of autoregulation [18].When the arterioles are obstructed, venous collapse ensues, followed by impaired CSF drainage and ventricular enlargement [18].

Evidence points also to an altered cerebral blood flow (CBF), which may favor such perivasal ischemia. It has been described a strong association between impaired CBF and iNPH. Patients with iNPH are more likely to have concomitant cerebrovascular disease [19]. MRI shows increased white matter changes (WMCs) [20] and this is further supported by neuropathological studies showing microvascular alterations [21, 22]. Age-related vascular changes can

directly cause the reduction in vascular compliance [23]; this could explain the association between NPH and vascular disease.

Alternatively, it has been proposed that increased transvenular resistance in the territory of the superior sagittal sinus can act as trigger in iNPH. Indeed, it might be that the majority of CSF resorption occurs through the brain parenchyma and not at the level of the arachnoid villi or arachnoid granulations [17, 24, 25]. In this view, CSF resorption would be affected with increased transvenular resistance.

CSF outflow resistance has been investigated in few studies, which reported an abnormal outflow in animal models and subjects with in iNPH [26, 27].

More recently, the new concept of glymphatic system has been introduced [28, 29]. The glymphatic system is a macroscopic waste clearance system which utilizes a unique system of perivascular tunnels formed by astroglial cells to promote the elimination of soluble proteins and metabolites from the central nervous system. It also facilitates brain-wide distribution of several compounds including glucose, lipids, amino acids, growth factors and neuromodulators; interestingly it functions mainly during sleep. The glymphatic system has been proposed to be instrumental in normal aging and brain pathology; in particular altered glymphatic function in iNPH could possibly be a mechanism behind the high comorbidity between iNPH and Alzheimer's disease [30]. A reduced glymphatic clearance has been found in a MRI study in iNPH and interpreted as instrumental for the development of dementia in this disease [29].

Further data suggest that aquaporin-4 channels can be implicated in the pathophysiology of iNPH [31]. Aquaporin-4 channels are transmembrane proteins that facilitate water transport in the brain and play roles in fluid secretion, cell migration, brain edema, metabolism, and many aspects of cell homeostasis; a modulation of their activity could be a potential target for pharmacological management of iNPH.

Lastly, also neurodegeneration might play a role in iNPH development as suggested by the high levels of tau protein in CSF of iNPH patients [32], as detailed below.

In conclusion, there is still a debate on the different theories of iNPH pathogenesis, even if it must be stressed that these theories may not be mutually exclusive [33]. Besides the possible mechanisms, it should be stressed out that many (although not all) of the clinical symptoms are reversible if patients are early recognized and correctly treated. The fostering of an early diagnosis is a great need, but must match the clinical accuracy.

3. Diagnostic considerations

Many other illnesses can mimic iNPH and therefore have to be distinguished. Regarding in particular the motor disturbances, the most frequent disease in differential diagnosis is Parkinson's disease; start hesitation and freezing episodes can occur in iNPH similar to the gait

in Parkinson disease, however rest tremor and usually unilateral symptoms onset typical of Parkinson's disease are less commonly observed in iNPH. Furthermore, in iNPH the response to the therapy with levodopa is usually scarce. The differential diagnosis can be particularly challenging in case of vascular dementia with small vessels disease or atypical parkinsonisms, Progressive supranuclear palsy in particular [34]. The differential diagnosis with AD will be treated below.

In their paper Williams, Relkin [1] report a precise analysis of differential diagnosis. Each of the primary symptoms of iNPH has in fact multiple potential etiologies (**Table 1**). It is quite uncommon to see patients affected by only iNPH because most of them have other conditions contributing to their symptoms. On the other hand, patients without iNPH may appear to have the iNPH syndrome because of multiple comorbidities.

	Gait	**Dementia**	**Incontinence**
Disorders that may have all 3 symptoms			
iNPH, with or without comorbidities	X	X	X
Parkinsonism	X	X	X
Lewy body dementia	X	X	X
Corticobasal degeneration	X	X	X
Progressive supranuclear palsy	X	X	X
Multiple system atrophy	X	X	X
Vascular dementia	X	X	X
Neurosyphilis	X	X	X
Medication side effects	X	X	X
Multifactorial—any combination of diagnoses, with or without iNPH	X	X	X
Disorders that may have 2 symptoms			
Multifactorial—any combination of diagnoses, with or without iNPH	X	X	X
iNPH, with or without comorbidities	X	X	X
Vitamin B_{12} deficiency	X	X	
Cervical stenosis and myelopathy	X		X
Lumbosacral stenosis	X		X
Peripheral neuropathy	X		X
Disorders that may have only one symptom			
iNPH	X		

	Gait	Dementia	Incontinence
Degenerative arthritis of the hips, knees, ankles	X		
Spinocerebellar degeneration	X		
Peripheral vascular disease (claudication)	X		
Alzheimer dementia		X	
Frontotemporal dementia		X	
Depression		X	
Hypothyroidism		X	
Sleep apnea		X	
Prostatic hypertrophy/obstructive uropathy			X
Pelvic-floor abnormalities			X
Interstitial cystitis			X
Disorders that can aggravate other symptoms			
Visual impairment	X	X	
Hearing impairment		X	
Obesity	X		
Cardiovascular disease	X		
Pulmonary disease	X		
Chronic lower-back pain	X		
Vestibular disorders	X		

Table 1. Differential diagnosis of idiopathic normal pressure hydrocephalus (iNPH). Taken from [1].

Initially is important to identify or exclude other disorders that should be treated before evaluating iNPH. Although iNPH is described as a symptom "triad," patients do not need to have all three symptoms. However, gait impairment is the symptom that affects nearly all patients as described by most published series and guidelines. A patient who has only dementia or incontinence should first be evaluated for other disorders. Patients with gait impairment and urinary symptoms but no cognitive impairment may need evaluation for spinal cord disorders. Although any of the primary iNPH symptoms may be the initial symptom, gait impairment is usually either the first or worst symptom.

http://dx.doi.org/10.5772/intechopen.73273

4. Management

Even though research in this field has advanced, iNPH still has to be considered a complex pathology whose diagnosis and management continue to present many problems. The main interest is represented by the fact that iNPH can be considered a potentially reversible dementia. Surgical diversion of CSF via a shunt remains the main treatment for this condition. This is based on the presumption that CSF diversion will reduce or normalize the transmantle pressure, thereby stabilizing or improving symptoms [14].

Ventriculo-peritoneal (VP) shunts are the most commonly used [35]; in Japan iNPH is treated mainly with lumboperitoneal (LP) shunts and in the last years also in Western Countries this procedure has began to be adopted. The data are still scarce, but LP shunts seem to have effectiveness rates similar to those of VP shunts. Despite greater rates of device-related complications, LP shunting can be recommended for the treatment of patients with iNPH because of their minimal invasiveness and lack of the lethal complications seen with VP shunts [36].

It must be stressed out that not all patients with iNPH are candidate for shunt surgery. The risk-to-benefit ratio has to be assessed individually. Prior to embarking upon surgical therapy, knowing which patients may benefit from surgery is necessary. All patients with suspected iNPH should undergo diagnostic CSF removal (either large-volume lumbar puncture and/or external lumbar drainage), which has both diagnostic and prognostic value. Detailed testing is performed before and after CSF drainage; improvement in motor symptoms after large-volume drainage supports the diagnosis of iNPH, while improvement does not rule out iNPH. Recently, a novel standardized paradigm with a simultaneous quantification of cognition and gait (dual task gait assessment and mental imagery of locomotion) before and 24 h after CSF tapping has been proposed [37], which can contribute to the identification of patients with iNPH from its mimics. The same authors underline the major limitation of this paradigm (i.e. an expansive and time-consuming evaluation), however it responds to the need of standardized evaluative parameters. Moreover, a levodopa challenge may be helpful to rule out idiopathic Parkinson disease; patients with iNPH have no significant response to levodopa or dopamine agonists.

The best candidates for shunt surgery would show imaging evidence of ventriculomegaly, indicated by a frontal horn ratio exceeding 0.30 on imaging studies, with one or more of the following criteria, as indicated by Schneck [38]:

- Presence of a clearly identified etiology.
- Predominant gait difficulties with mild or absent cognitive impairment.
- Substantial improvement after CSF withdrawal (CSF tap test or lumbar drainage).
- Normal-sized or occluded sylvian fissures and cortical sulci on CT scan or MRI.
- Absent or moderate white matter lesions on MRI.

Specific criteria and guidelines have been defined for the surgical procedure and the post-operative and long-term care, including the management of complications [7, 9], even if a consensus measurement of CSF shunting outcome is still lacking [14].

Many studies have investigated the benefit of shunt surgery. Only one assessed the benefit of shunting surgery in a randomized manner and showed that, among the 14 patients included, only those with CSF shunts improved at 3 months follow-up. In particular, the patients with effective (open) shunts showed an improvement in motor and psychometric scores (30 and 23% increase, respectively) at 3 months, whereas those with placebo (ligated) shunts were unchanged. Of note, this latter group also improved after opening the shunts, although with less benefit (28 and 18%, respectively) [39].This rate of benefit is in line with the results of a systematic review, which reported a long-term response of 29% [40]. A double-blind randomized trial on the clinical effect of different shunt valve settings was also performed [41]; improvement after shunt surgery was evident within 3 months, irrespective of valve setting.

Recent studies showed higher rates of success (around 80–90%) [42, 43]; all these outcomes must be interpreted with caution, given the lack of standardized method of comparison. Besides the possible benefit, information about the risks of complications should also be provided, since they appear to be very common [44].

The complication ratio of CSF shunt was found on average of 38%. Potential complications include infection, seizures, abdominal problems (peritonitis, perforation, volvulus, and ascites), shunt failure or blockage, shunt over-drainage and intracranial hemorrhage. The most common complication was the shunt over-drainage occurring in up to one-third of the patients within the first year [40]. Of course, the complication rates differ across centers. The Eu-iNPH study revealed a complication rate of 28% [42], while a recent study over more 230 subjects found a complication rate of less than 12% [43].

In any case, the clinical follow-up of the patients is essential. The follow-up helps the management of the complication, identifying the patients who need adjustments or revision of the shunt. Repeated brain imaging is usually performed after shunting and can support the identification and early treatment of subdural hemorrhage [14].

As previously reported, the response to levodopa/carbidopa is absent or scarce. In patients who are poor candidates for shunt surgery, repeated lumbar punctures in combination with acetazolamide may be considered [45]. Recent studies on aquaporin-4 channels suggest interesting perspectives for future pharmacological treatment of iNPH [31].

5. Cognitive impairment in iNPH

The cognitive and behavioral disturbances accompanying iNPH have been commonly described as “fronto- subcortical dementia” [46, 47]. This clinical term is used to refer to a pattern of mental decline, characterized by executive dysfunction, psychomotor slowing and mood symptoms,

especially apathy [48, 49], that is often present in patients with iNPH. However, as it will be detailed in this chapter, a wide range of other cognitive disturbances beside frontal involvement can be detected.

Boon et al. [26] in a study evaluated global cognitive functioning, memory, and attention in a large sample (101 patients), reported that iNPH patients showed severe impairment of attention and psychomotor speed.

Iddon et al. [50], on the basis of Mini-Mental State Examination (MMSE) score cutoff, divided their sample of 11 patients into two groups: demented and non-demented. By the means of neuropsychological instruments which evaluated different cognitive functions, two cognitive profiles in iNPH have been identified, one observed in patients at a less advanced disease stage, who presented isolated frontal lobe dysfunction, and the other observed in those who have reached a more advanced stage and presented severe global cognitive dysfunction. The non-demented iNPH patients obtained a worse performance on attentional tasks, thus suggesting a deficit in cognitive flexibility, similar to patients with frontal lobe excision and patients with fronto-subcortical dementia such as Parkinson's disease [51, 52], and unlike patients with AD in which frontal functions usually are spared [53].

Ogino et al. [46], in a well-controlled study, analyzed 21 patients with iNPH and 42 patients with AD, using a neuropsychological assessment investigating different cognitive domains. iNPH patients had more severe impairment of attention, psychomotor speed and calculation than those with AD, while memory function and orientation were more preserved. Impairment in frontal functions in iNPH, but not in AD, was reported also by Miyoshi et al. [54], who compared the scores recorded on the Frontal Assessment Battery (FAB), on verbal fluency subtests and on subtests of the MMSE in patients with iNPH and AD, matched for age, sex, and MMSE score.

Tarnaris et al. [47], analyzing cognitive performances of 10 patients with iNPH through a complete neuropsychological assessment (language, memory, executive functions, visuospatial abilities, and attention), confirmed that all the patients had subcortical cognitive impairment, characterized in particular by dysexecutive dysfunction and slowed mental processing.

Therefore, some studies have tried to relate the cognitive impairment in iNPH to damage the frontal lobe The results of single photon emission computed tomography and positron emission tomography (PET) studies showed that iNPH patients mainly presented hypoperfusion of the frontal lobe [55–57].

On the basis of the finding that periventricular white matter cerebral blood flow was reduced in iNPH [56] it has been suggested that the frontal lobe dysfunction might be secondary to a disturbance of the subcortical area connecting with the frontal lobe cortex [50, 57, 58]. The relatively preserved memory and orientation functions may be explained by a lower involvement of memory systems, including the medial temporal lobe, in iNPH than in AD [46]. However, a neuroimaging study [59] demonstrated a reduction in the medial temporal volume in iNPH. Parietal regional cerebral blood flow reduction in iNPH has also been shown in other neuroimaging studies [60, 61].

On the other hand, other studies have demonstrated that patients with iNPH can be impaired in broader cognitive domains; the definition of fronto-subcortical dementia has therefore to be considered reductive, given that the cognitive deficits observed in iNPH can extend beyond executive function, attention, working memory, and episodic memory to visuoperceptual and visuospatial functions [26, 56, 62, 63].

Saito et al. [64] evaluated 32 iNPH patients, 32 AD patients and 30 healthy elderly controls, using an extensive and comprehensive neuropsychological battery to investigate all the different cognitive domains: language, memory, executive functions, visuospatial and visuoperceptual abilities, attention, and mental processing speed. Their results suggested that iNPH is associated with impairment in various aspects of cognition involving both frontal-executive and posterior-cortical functions, such as visuoperceptual and visuospatial abilities. In particular, defective performances were found on the visual discrimination and visual counting tasks; visuoperceptual and visuospatial abilities in iNPH patients were more severe than in those with AD, whereas the degree of memory impairment was comparable to that in AD patients.

The main involvement of visuospatial functions was observed also by Bugalho et al. [65]; 17 iNPH patients have been compared with 14 healthy controls and the authors suggested that visuospatial deficits, and not executive dysfunction, could be an early sign of cognitive deterioration in iNPH patients regardless of the severity of global cognitive dysfunctions.

Some studies, instead, focused on the nature of the memory deficit in order to identify a specific pattern. Walchenbach et al. [63] analyzed 51 iNPH patients, administering the MMSE and neuropsychological tests assessing both cortical (language, visuoperceptual skills and praxis, and memory functions) and fronto-subcortical functions (mental speed, concept shifting, and abstract reasoning). They suggested that the pattern of memory deficit in iNPH is of the frontal lobe type, in which recall is disproportionately affected with respect to recognition, while in patients with AD recall and recognition are both impaired. Ogino et al. [46] observed memory impairment in iNPH, but they found that impairment of executive functions was more severe, while impairment of memory and orientation was milder in patients with iNPH than in those with AD. On the contrary, Saito et al. [64] found that both recognition and recall were impaired in a similar fashion both in iNPH and AD groups, thus suggesting that memory impairment in iNPH is not exclusively ascribable to frontal lobe dysfunction.

Therefore the data of the literature seem to confirm a wide range of cognitive decline in iNPH patients and according to Devito et al. [66] we can conclude that: "in some cases it may be qualitatively similar to normal aging, in others it may manifest as progressive dementia with gait disturbance, clinically similar to Alzheimer's or Parkinson's disease".

However, there is no general agreement on the neuropsychological instruments to be used in assessing cognitive deficits. Bugalho et al. [65] employed a cognitive assessment protocol focused on various cognitive domains (global cognitive function, verbal memory, impulse control, verbal fluency, working memory, attention, visuospatial reasoning, and visuoconstructive abilities) and also on mood and hand dexterity. Devito et al. [66] in a not recent but very interesting paper have reviewed possible application of clinical neuropsychology and

how it has contributed to our understanding of cognition in iNPH; they proposed a clinical assessment protocol in which beside cognitive evaluation a great importance was attached to the evaluation of emotional domains, apathy and depression in particular, and quality of life.

Ogino et al. [46] assessed cognitive functions by administration of the Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised, and Alzheimer Disease Assessment Scale (ADAS) orientation subtest. Saito et al. [64] used an exhaustive and detailed neuropsychological assessment, which included the MMSE for general cognitive function, Digit Span and Spatial Span for attention, Word fluency, Trail Making Test A (TMT A) and FAB for executive function, Object naming subtest for language, the Word recall and Word recognition subtests of ADAS for episodic memory and Visual discrimination, Overlapping figures and Visual counting tasks for evaluating visuoperceptual and visuospatial functions.

In a recent study by Missori and Currà [67] all the patients underwent a wide neuropsychological assessment: MMSE, FAB, Rey's 15 words immediate and delayed recall, Wisconsin Card Sorting Test, TMT, Attentive Matrices, Analogies test, and Digit Span forward and backward tasks. However, the authors included only the scores from the MMSE in the analysis of the results because the aim of their work was to grossly quantify cognitive impairment in patients.

As we can see, most authors have used large neuropsychological battery, but different measures within the single cognitive domain have been administered in the different studies. Therefore the various studies are not immediately comparable and a standardized protocol should be needed.

6. Cognitive impairment after shunt surgery

iNPH is considered a potentially reversible dementia and as described above the treatment of choice is ventriculo-peritoneal or atrial shunt device placement. When considering the global outcome, there is a general agreement about the fact that short-term results are more likely to be influenced by shunt-associated risks, while long-term results are more influenced by other factors, such as concomitant neurodegenerative and cerebrovascular diseases; the one-year post-shunt period can be considered a determinant of long-term results of the treatment [68].

Shunt surgery can help to reduce cognitive impairment, especially if it is performed during the early stage of deterioration, as it will be more detailed below; if the pressure is not relieved quickly by a shunt patients with severe iNPH will in fact develop overall cognitive impairment [9, 50]. This deterioration is only partially reversible as reported by Andrèn et al. [69], who described the effects of waiting for at least 6 months before surgery and compared the outcome with that seen in patients who waited for less than 3 months. The patients of the first group significantly deteriorated; both groups ameliorated at the same size after surgery, but since the symptoms of the patients of the first group had worsened while waiting, their final outcome was significantly poorer.

Indeed, most studies report an improvement after surgery, but there is no general agreement neither about cognitive functions are more likely to be restored after shunt placement nor about possible indicators with a predictive value.

Iddon et al. [50], as already mentioned, studied 11 patients (5 demented and 6 non-demented); the demented patients showed a significant improvement after shunt surgery, whereas in the not demented patients who presented frontal deficits no improvement could be detected. The same authors suggested that even successful shunt surgery may not alleviate all aspects of cognitive impairment.

Thomas et al. [70] reported that verbal memory and psychomotor speed appear to be the functions more likely to respond to shunt surgery; 22 (53.2%) out of 42 patients at least 3 months after surgery showed an overall cognitive improvement (defined as a four-point improvement on MMSE or an improvement by 1 standard deviation in 50% of the neuropsychological tests) and a significant improvement in tests of verbal memory and psychomotor speed. However, in patients who, at baseline, presented impairment of both verbal memory and visuoconstructive functions, the cognitive improvement was less pronounced; on this basis the authors suggested that baseline cognitive scores may distinguish patients responsive to surgery, that is, the greater the impairment the smaller the recovery. Other studies report an improvement of memory, frontal lobe, and visuoconstructive functions at 6 months [71] and 1 year [62] after shunt surgery; in the paper by Mataró et al. [71] a concomitant significant increase in the global corpus callosum size on MRI was also reported.

In a series of 47 consecutive patients, Hellstrom et al. [72] reported that most of the wide range cognitive functions are typically affected in iNPH improved at 3 months after shunt placement; contrary to the study by Mataró et al. [71] the more severe functional deficits showed the greatest improvements, although they were not completely restored to the levels present in healthy controls.

Saito et al. [64] found that frontal functions (assessed using the TMT and FAB) were improved at 1 year after the shunt procedure in 26 out of 32 patients; the authors excluded that the improvement observed could be ascribed to a possible practice effect. Actually, this is an important question which can occur when patients are evaluated after a short interval of time.

Other studies have followed the patients for a longer period, identifying as outcomes the evolution toward dementia and the survival. Koivisto et al. [73] in a study with a median follow-up of 4.8 years, found an increased risk of dementia and cognitive decline even in patients who had initially responded to the shunt. At the end of the follow-up period, 117/146 (80%) had cognitive decline and 67/146 (46%) clinical dementia, mainly AD and vascular dementia. In a multivariate analysis, memory deficit as a first symptom emerged as a predictor of dementia. Interestingly, eight (5%) patients who at baseline had the full triad of symptoms presented dementia without any other signs of neurodegenerative or vascular disease.

Golz et al. [74] followed up 147 patients for 6 years after surgery through yearly examinations; 69 died during the follow-up, 61 reached the six-year assessment. Of these 61 patients, 59% had an excellent outcome, 15% satisfactory benefit, and 26% unsatisfactory results. The authors concluded that shunt surgery can be considered a safe procedure with a favorable

outcome. However, no cognitive evaluation was performed; the patients were evaluated using only a specific scale for iNPH and a Comorbidity Index to account for additional diseases, which could influence the clinical presentation and outcome.

In some studies the response to shunt has been related to the presence/absence of findings consistent with Alzheimer pathology on cortical biopsy or CSF sampling, but the results are contradictory. Golomb et al. [75] at a mean post-shunt follow-up of 4.3 months, found a small but significant improvement in tests of attention and processing speed only in patients with a cortical biopsy negative for Alzheimer pathology. These data were confirmed by Savolainen et al. [76], who studied 51 patients under 75 years of age with possible iNPH; 25 of these patients underwent shunt surgery. One year after shunt placement, 72% of the patients showed a good recovery in activities of daily living, 58% experienced improved urinary incontinence, and 57% walked better; the positive effects of the shunt were still present at 5 years. However, no change on neuropsychological test performances was found, leading the authors to conclude that neuropsychological evaluation, and the MMSE in particular, is of little value in diagnosing iNPH. Eight patients with shunt and nine without shunt died in the course of the five-year follow-up. The patients with a positive biopsy for Alzheimer pathology had worsened more than those with a negative biopsy after 1 year, but mortality was not increased in these patients.

On the contrary, Pyykko et al. [77] did not find any differences in CSF Aβ levels or tau biomarkers between shunt-responding and non-responding iNPH patients, the latter, however, were older; no identification of a cognitive profile was identified as no formal neuropsychological evaluation was performed in order to better define the response to shunt placement.

The same results have been obtained by Yasar et al. [78] the presence of AD pathology in 26% of the population with iNPH did not significantly influence the clinical response to shunt surgery.

Some studies have focused on the caregiver, interpreting a change of caregiver burden as an indirect sign of clinical/cognitive modification. A decrease in caregiver burden was reported by Kazui et al. [79] in the caregivers of 81 iNPH patients 1 year after the patients underwent the shunt procedure; the improvement of cognitive impairment was identified as the major factor contributing to the reduced caregiver burden, even though a formal neuropsychological evaluation was not performed.

Petersen et al. [80] evaluated the impact of shunt surgery on social function and health-related quality of life in 37 patients 6 months after the procedures; non cognitive evaluation was performed. Twenty-four (65%) showed a clinical improvement, while in 31(86%) quality of life returned almost within normal range as a consequence of their greater independence. Despite these good results, the caregiver burden was reduced only in caregivers to male patients.

In order to better understand the mechanisms underlying iNPH, some authors looked for correlations between cognitive changes and metabolic functioning in specific cerebral regions. Calcagni et al. [81] performed F-FDG PET/CT scanning 3 days before and 1 week after shunt placement in a small group of iNPH patients. After surgery the global glucose rate significantly increased in all patients, while the ventricular size did not change. Clinical status and

independence in daily life was measured using scales evaluating activities of daily living, gait, urinary incontinence, cognition (the modified Rankin scale, the Krauss scale, the Larsson categorization system, the Stein-Langfitt scale); a relationship between functional data and clinical assessment was found only after surgery, not before, while changes both in FDG uptake and in global cognitive functioning measured by MMSE were reported in 3 out of 19 subjects. A further study by the same authors [82] confirmed these data. In an earlier study, Dumarey et al. [83] observed an improvement of regional blood flow in the bilateral dorsolateral frontal and left mesiotemporal cortex in patients who had previously seen to be clinical responders to the spinal tap test. All these data show that functional changes occur early than morphological ones and seem to suggest a prompt metabolic response by neuronal cells possibly related to neuronal plasticity. As yet, however, functional imaging does not seem to provide prognostic information making it possible to identify patients who will benefit from surgery.

7. iNPH and Alzheimer's disease

As above reported iNPH can mimic other neurological diseases variously characterized by gait disturbances and cognitive impairment, namely vascular dementia with small vessel disease, dementia with Lewy bodies, Parkinson's disease and other parkinsonisms. The diagnostic differentiation can be difficult. In this regard, clinical and neuroimaging data are crucial; also the lack of response of iNPH patients to antiparkinsonian drugs can help in the diagnosis.

As regard AD, the matter is fairly complex and challenging. Motor disturbances are usually absent in AD, at least in the early stages. As for cognitive impairment, as explained in the previous section, impairment of frontal lobe-related functions is not frequent in AD, even if a "frontal" variant has been described [84]; all types of memory are impaired in AD, while recognition memory is relatively preserved in iNPH. On the other hand, an overlapping of the two diseases cannot be excluded, this is particularly important when considering the response to shunt surgery. From this perspective, many studies have tried to identify biological markers both for improving the diagnosis and predicting shunt efficacy.

Savolainen et al. [76] performed cortical biopsy in 223 iNPH patients; 66 subjects presented normal brain tissue, while Alzheimer pathology (neuritic plaques) was present in over 40% of patients. The authors suggest that these data may explain the unsuccessful recovery of many patients after shunt surgery. The presence of positive biopsies for neuritic plaques was also reported by Golomb et al. [75]; 81/117 patients with possible iNPH received a structured psychiatric interview, out of these 81, 77 were cognitively impaired (Global Deterioration Scale- GDS, ≥ 3), out of these 77, 56 received cortical biopsy. Twenty-three patients presented neuritic plaques; these subjects with positive biopsies were more cognitively impaired (higher GDS and lower MMSE scores) as well as more gait impaired than patients with negative biopsies. The prevalence of neuritic plaques increased in parallel with dementia severity from 18% for patients with GDS = 3–75% for patients with GDS scores >6. However, in this study the concomitant Alzheimer pathology did not strongly influence the clinical response to shunt surgery independently by the severity.

On the contrary, the degree of Alzheimer pathology is reported to be important in predicting the response to surgery in the study by Hamilton et al. [85]; out of 37 patients 12 showed a negative biopsy, the remaining 25 subjects showed a high percentage (above 60%) not only of neuritic plaques but also of neurofibrillary tangles, which indicates the presence of tau pathology. Patients with moderate-to-severe Aβ and tau pathology showed more severe baseline cognitive impairment and poorer performance postoperatively on NPH symptom severity scales and measures of cognition, while patients with mild Alzheimer pathology responded well to shunting. The authors suggest that some patients may be relatively unimpaired by the presence of cortical Alzheimer pathology; the different results obtained in respect to previous studies are explained by the different methods employed.

Leinonen et al. [86] evaluated the predictive value of brain biopsy for the long-term outcome of iNPH in 468 patients with possible iNPH; the presence of beta-amyloid was detected in 197 (42%) patients, and together with tau pathology in 44 cases (9%), but it did not affect the survival.

On the other hand, Alzheimer pathology as neuritic plaques can be present also in the brain of normal healthy individuals [87]; therefore, in order to ameliorate the differentiation of diagnosis, also CSF biological markers have been investigated. The specific combination of both low CSF beta-amyloid (Aβ)-42 and elevated CSF phosphorylated tau (P-tau) in fact is considered the biological signature of Alzheimer's disease, where low Aβ levels reflect amyloid deposition and high tau levels indicate a prevalent non specific neuronal damage [88].

In 2007, Kapaki et al. [89] studied 85 patients subdivided in 67 with AD and 18 with iNPH, and 72 healthy controls. Aβ-42 levels were significantly decreased in both diseases as compared with controls, while P-tau levels were significantly increased only in Alzheimer's patients; therefore the authors concluded that P-tau may be a useful marker in the differentiation of iNPH from Alzheimer's disease.

In the same year Agren-Wilsson et al. [90] studied 62 iNPH patients, 26 patients with subcortical vascular encephalopathy and 23 healthy controls. The CSF concentration of neurofilament light protein was elevated in iNPH and vascular encephalopathy compared with the controls, levels of total tau (T-tau), P-tau, and Aβ-42 were lower in iNPH compared with vascular encephalopathy and controls; all markers except Aβ-42 were significantly elevated after shunt surgery. These results lead the authors to conclude that not a specific marker but the combined pattern of more markers can distinguish iNPH from vascular patients and controls.

Lower CSF levels of both T-tau and P-tau and amyloid precursor protein have been reported also by Jeppsson et al. [91] in 28 iNPH patients compared with 20 healthy controls, while neurofilament light protein was elevated. After surgery there was an increase; these data have been interpreted as due to a reduced periventricular metabolism and axonal degeneration rather than to a major cortical damage.

Kang et al. [92] found lower CSF Aβ-42 levels and lower P-tau levels in 35 iNPH patients in respect to the control reference values; tau levels correlated with gait disturbance and CSF P-tau/Aβ ratios were significantly higher in patients who did not respond to shunt surgery.

Jingami et al. [93] studied 55 iNPH patients, 20 Alzheimer's disease patients, 11 patients with cortico-basal syndrome, and 7 patients with spino-cerebellar degeneration. Tau levels were significantly decreased in iNPH in respect to AD especially in tap test responders patients; the authors concluded that CSF tau can be considered useful for differentiation iNPH from AD.

Pyykkö et al. [77] performed both cortical biopsy and CSF sampling in a population of 53 patients with iNPH, 26 with AD, and 23 with other diagnosis. In iNPH Aβ load in the brain biopsy showed a negative correlation with CSF levels of Aβ-42, no differences in markers of neuro-inflammation and neuronal damage were found in both iNPH and Alzheimer's patients. No differences between CSF Aβ levels or tau biomarkers in shunt-responding and non-responding iNPH patients have been reported, the non-responding patients were however older.

The results of a recent meta-analysis [94] suggest that iNPH may be associated with significantly reduced levels of CSF Aβ42, t-tau and p-tau compared to normal controls, while compared to AD both t-tau and p-tau were significantly decreased in iNPH, but CSFAβ42 is slightly increased. The data cannot be considered definitive and helpful for the diagnosis and the authors conclude that prospective studies are needed to further assess the clinical utility of these and other biomarkers in assisting in the diagnosis of iNPH and differentiating it from AD and other neurodegenerative disorders.

Actually iNPH CSF profile seems to be different from AD, in particular most studies report low CSF tau levels which are in contrast with elevated CSF tau levels in AD. However, the results from the literature cannot be considered conclusive. With particular regard to the data pre- and post-shunt Graff-Radford [95] observe that CSF biomarkers cannot be considered helpful in distinguishing patients with iNPH from those with comorbid AD and rather can provide misleading information. The author suggests that the pre-shunt low CSF Aβ42 (and other APP fragments) are not necessarily related to Aβ brain deposition similar to what happens in AD, but rather could be result from impaired clearance; the data of pre-shunt low tau proteins levels may have the same explanation. In iNPH in fact the brain is compressed and therefore a decrease in interstitial space and APP protein fragment drainage into the CSF may be impeded, resulting in low levels of all CSF proteins. Shunting decompresses the brain and creates more room for the interstitial space to increase and protein waste fragments to drain into the CSF; CSF proteins increase after shunting in fact has been reported. On the other hand Graff-Radfford [95] remarks that this hypothesis does not exclude the hypothesis proposed by Jeppsson et al. [89] about a reduced periventricular metabolism; prospective amyloid PET studies could be needed in order to determine whether this procedure is able to distinguish iNPH from comorbid AD.

8. Our experience

As reported in our recent review [96] the classic definition "fronto- subcortical dementia" is reductive, because it cannot completely describe the entire clinical spectrum. It is now known

that patients with iNPH actually present impairment in broader cognitive domains: attention, working memory, episodic memory, visuoperceptual, and visuospatial functions [50, 63–65].

Here we report the results of our experience [97] to confirm this hypothesis. We evaluated retrospectively the cognitive profile and its relationship with disease variables in a group of subjects with iNPH. We retrospectively studied clinical charts collected from January 2010 to December 2014, at the Parkinson's Disease and Movement Disorders Unit of the Istituto Neurologico Nazionale "C. Mondino" of Pavia, Italy. A case series of 64 subjects with diagnosis of "probable" iNPH was collected. All recruited patients were referred with primary diagnoses of "parkinsonism".

The diagnosis of iNPH was made on the basis of clinical, neuropsychological and neuroimaging features [1]. In particular, as regard neuroimaging, we followed the criteria previously reported: ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evans Index >0.3) and the absence of macroscopic obstruction to CSF flow. These main aspects had to be accompanied by at least one of the following supportive features: enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy; narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface; callosal angle of 40° or more; evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination; an aqueductal or fourth ventricular flow void on MRI.

Evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus has been excluded as well as other neurologic, psychiatric, or general medical conditions sufficient to explain symptoms.

Fifty-eight healthy elderly, matched for age, sex, and education, recruited among hospitalized patients and/or patients' relatives without neurological disorder or cognitive impairment, represented the normal control group (NC). All patients and NC were examined by a neurologist and tested by a neuropsychologist.

Motor symptoms have been evaluated by the Unified Parkinson's Disease Rating Scale Part III (UPDRS III); this scale has been currently applied to measure the motor impairment due to parkinsonism and is administered by the clinician [98, 99].

The following neuropsychological tests were administered to evaluate various domains of cognition:

- Mini-Mental State Examination (MMSE): general index of cognitive functioning
- Digit Span forward, Word Span and Spatial Span (Corsi's test) tests: working memory
- Rey's 15-word test, both immediate and delayed recall: long-term verbal memory
- Logical memory test: long-term verbal memory for structured material
- Raven's Colored Matrices 47: visuospatial reasoning
- Weigl's Sorting Test: categorical abstract thinking

- Frontal Assessment Battery (FAB): fronto-executive functioning
- Attentive matrices: selective attention
- Phonological and semantic fluency: lexical magazine
- Constructive Apraxia: copying and visuospatial abilities.

Age-, gender-, and education-corrected scores were calculated from the raw scores; the corrected score then were transformed into equivalent scores, ranging from 0 (pathological) to 1 (lower limit of normal) and 2, 3, 4 (normal).

As reported in **Table 2**, compared to normal group, iNPH patients showed a worst cognitive performances in almost all neuropsychological tests, except for Rey's 15-word test, immediate recall, and Logical memory test, which were within the normal range (ANOVA).

Test/subtest	iNPH	NC	P value
Subjects F/M	64 29/35	58 26/32	
Age (years)	73.7 ± 7.5 (range 66–81)	76.0 ± 5.8 (range 71–81)	NS
Education (years)	8 ± 5	8 ± 5	NS
Disease duration (months)	40.1 ± 31.8 (range 8–71)		
MMSE	21.8 ± 4.9	28.5 ± 1.5	0.000000001
Digit span forward	4.4 ± 0.7	5.1 ± 1.3	0.0008
Word span	3.8 ± 0.7	4.2 ± 0.9	0.01
Spatial span (Corsi's test)	3.4 ± 1.0	5.0 ± 1.3	0.00000002
Rey's 15-word test	31.2 ± 7.5	33.1 ± 2.4	NS
• Immediate recall	4.7 ± 3.6	7.1 ± 2.3	0.0001
• Delayed recall			
Logical Memory test	6.9 ± 4.3	8.2 ± 3.4	NS
Raven's Colored Matrices 47	21.0 ± 6.6	25.1 ± 5.3	0.0007
Weigl's Sorting Test	5.9 ± 2.9	7.2 ± 2.1	0.01
Frontal Assessment Battery (FAB)	11.5 ± 3.6	15.6 ± 1.8	0.00000008
Attentive matrices	34.8 ± 12.1	42 ± 6.9	0.0003
Verbal fluency:	19.9 ± 9.2	23.1 ± 4.3	0.02
• Phonological	12.1 ± 3.4	14.0 ± 2.6	0.002
• Semantic			
Constructive Apraxia	10.9 ± 2.6	12.1 ± 1.9	0.009

Table 2. Demographic and neuropsychological profiles: Comparisons between iNPH and NC groups (M ± SD) (ANOVA)].

http://dx.doi.org/10.5772/intechopen.73273

When considering the different cognitive domains involved and on the basis of equivalent scores, we subdivided the entire iNPH population in the following subgroups:

- Group 1 (G1): 27 patients (42%) with global cognitive impairment, characterized by global deficit of cognitive functions, or anyway by widespread deficit.
- Group 2 (G2): 15 patients (24%) with typical deficit in attention and executive abilities (fronto-cortical dysfunction).
- Group 3 (G3): 11 patients (17%) with mild cognitive impairment (MCI), single domain (isolated deficit of a single cognitive domain, i.e. memory, attention, visuospatial abilities).
- Group 4 (G4): 11 patients (17%) with no cognitive impairment.

In **Table 3**, the clinical, demographic, and motor characteristics of the different groups are reported (Chi square test).

In G1 the patients were older, with significantly longer disease duration and a more severe motor impairment in respect to the other groups ($p < 0.00001$). UPDRS III total score showed significant differences between G2 versus G3 and G4 patients ($p < 0.02$ and $p < 0.0001$, respectively). No differences were found between G3 and G4 groups.

The results of this study show that, when comparing with controls, our iNPH whole population was impaired in almost all neuropsychological measures; the extent of statistical significant varied from test to test, being more pronounced in logical and executive functions. Only episodic memory was relatively preserved; these data seem to suggest that memory impairment in iNPH is generally milder in respect to the deficit in other functions, executive in particular [46].

However, when we consider the different cognitive domains involved, we can identify subgroups of patients with different cognitive profiles: about an half of the subjects (42%) in fact presented an overall diffuse impairment which can be framed as dementia of mild to moderate

	G1	**G2**	**G3**	**G4**
	Global cognitive impairment (27 pts)	**Fronto-cortical dysfunction (15 pts)**	**MCI single domain (11 pts)**	**No cognitive impairment (11pts)**
Sex M/F	13/14	10/5	7/4	5/6
Age (years)	79.3 ± 1.9*	73.7 ± 7.5	70.4 ± 4.2	69.9 ± 3.2
Disease duration (months)	54.2 ± 16.8*	40.0 ± 31.0	33.3 ± 13.2	32.4 ± 11.3
UPDRS III	36.6 ± 10.0*	26.3 ± 3.1°+	20.6 ± 8.4	21.4 ± 2.3
	range 47–27	range 29–22	range 29–10	range 24–16

*G1 vs. G2, G3 and G4: $p < 0.00001$; °G2 vs. G3: $p < 0.02$; +G2 vs. G4: $p < 0.0001$.

Table 3. Demographic and clinical characteristics of the different iNPH groups (M ± SD) (ANOVA).

degree, out of not demented patients, only 24% was characterized by fronto-cortical dysfunction and we also found a subgroup with impairment in a single cognitive domain and even patients without any neuropsychological deficit.

Therefore our results are in agreement with the data of the literature about a wide range of cognitive pictures in iNPH [50, 63–65, 94]; in particular, the heading of "fronto-subcortical dysfunction" is reductive as it cannot completely encompass the different cognitive profiles.

The second important finding of our study is represented by a positive correlation between cognition and disease progression; in fact, though cognitive impairment may be absent in early cases, its severity undoubtedly increases with older age, disease duration and severity of motor disturbances, hypothesizing an underlying common physiopathological mechanism. In this view, as our data can suggest, an early shunt surgery could contain not only the progression of motor disturbances but also the advance of cognitive impairment in these patients.

Our sample was enrolled on the basis of the presence of gait disturbances/parkinsonism and because of these symptoms the patients were referred to our Unit; this aspect may represent a weakness of the study in term of patient's enrollment. On the other hand it is well-known that motor disorders are the leading presentation of iNPH [1].

In this study, we have administered an exhaustive neuropsychological evaluation in order to investigate different cognitive domains; this is crucial to obtain a more detailed cognitive profile, as suggested by different authors [64–66]. In our opinion an accurate cognitive characterization before shunt is relevant in terms of outcome measures. Enrolling homogeneous population of iNPH may improve the prediction of response to shunt surgery; a longer follow-up period and a closer interaction among the different professionals are needed.

9. Conclusions

iNPH remains a complex and underestimated disease. As far cognitive impairment, this has commonly been described as fronto-subcortical dementia, but on the basis of the data of the literature we can assume that this term is reductive as it does not fully describe the different clinical pictures observed with an involvement of many other cognitive domains. Even after many years we still agree with the remarks of Iddon et al. in 1999 [50] "There may not be one single form of dementia syndrome in NPH but rather, there are varying degrees of cognitive change pre-shunt, according to the amount of permanent brain damage that has already taken place, compounded by comorbidity factors such as hypertensive cerebral small vessel disease". Undoubtedly, many other variables differently modulate and interfere with the disease expression. Moreover, an overlap with other neurodegenerative diseases can exist; this may be a complex and prognostic issue and could partly explain both the progression of cognitive decline and the absence of amelioration after successful CSF shunt procedures. With regard to the possible overlap with AD in particular, the weight of Alzheimer pathology in iNPH patients is not clear; studies investigating possible biological markers in fact have failed to obtain conclusive results.

The great variability of clinical pictures in iNPH has to be interpreted also taking into account the role of the "cognitive reserve" phenomenon [100]; even partially, this aspect can also contribute to the differences of the response to shunt surgery.

Clinical and neuroimaging data are crucial for the diagnosis and the literature has provided guidelines and precise neuroradiological diagnostic criteria. However, there is no general agreement about the neuropsychological measures to employ in assessing the condition, as the studies reported in the literature used different cognitive tests; this aspect is obviously relevant to the post-shunt follow-up, too. The neuropsychological assessment has to include sensitive and exhaustive measures investigating the different cognitive domains; also patients' quality of life and caregivers' point of view have to be investigated in particular after shunt surgery in order to obtain a more global and sensitive evaluation.

Another important issue is represented by the difficulty to establish with precision the different stages in the disease. The studies reported in the literature have been conducted in patients with different disease durations and therefore with different degrees of disease severity; this makes it difficult to compare the different results and obviously the results after shunt placement may well be negatively affected in patients with more severe or longer lasting disease. In particular as regards the shunt procedure, reliable indices predictive of a good response to surgery are still lacking; in the studies analyzed different outcome measures were employed in different follow-up periods.

We can conclude that there is a need for further studies with a better standardization; longer follow-ups and closer interaction among the different professionals involved are also requested.

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Medical Treatment

Chapter 5

Hydrocephaly: Medical Treatment

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73668

Abstract

Hydrocephaly is a prevalent condition in all age groups. At present, the most frequent strategies used to treat hydrocephaly are surgical shunting procedures, which are still associated with multiple complications. The main goal of the medical therapy for the lowering of high ventricular pressure is to avoid shunting or to reduce and decrease intracranial pressure (ICP) until shunt surgery. Medications affect cerebrospinal fluid dynamics by decreasing secretion or increasing reabsorption. Medical treatment for manipulation of water balance or cerebrospinal fluid (CSF) production reduces mortality in both infants and adults with neurological disorders. Medical treatment has an important role in the management of hydrocephaly especially in patients not suitable for shunt and in patients whom the shunt alone is not able to control the hydrocephaly. The treatment is used to delay surgical intervention but is not effective in the long treatment of chronic hydrocephaly.

Keywords: hydrocephaly, intracranial pressure, drugs, treatment, acetazolamide

1. Introduction

Hydrocephaly is an increased volume of cerebrospinal fluid (CSF) in or around the brain that can be produced by various disorders [1]. CSF accumulation mostly occurs within ventricles, but the accumulation may occur in other sites of the brain. It can develop at any age, both in infants and in adults [2]. The cumulative 5-year complication rate was reported approximately 48% in children and 27% in adults, in a large population-based analysis in California in the 1990s [3]. According to the studies, approximately 3.4 per 100,000 per year in the adult population undergo a surgical procedure for hydrocephaly. In infants, symptoms include a large and rapidly growing head, bulging, irritability, and seizures. In adults and children,

symptoms are headache, difficulty in walking, lossing the ability in hard activities, decrease in mental abilities, vomiting, and lethargy. A headache may even awaken the patient from sleep in case of increased intracranial pressure (ICP). Papilledema is more common in adults than children.

Hydrocephaly can be classified according to the site of CSF flow obstruction or impairment as internal hydrocephaly CSF accumulation which occurs in ventricles and external hydrocephaly in which the accumulation of CSF occurs in subarachnoid space in cerebral cortical surfaces. Hydrocephaly is classified into two groups according to its cause: communicating and noncommunicating hydrocephaly. In communicating hydrocephaly, CSF flows from lateral ventricles into cerebral and spinal subarachnoid space (SAS). In contrast, noncommunicating hydrocephaly flow of the CSF through ventricles is interrupted for any reason. The obstruction of CSF flow in noncommunicating hydrocephaly may happen either internal or external to the ventricles. On the other hand, the overproduction of CSF may cause an accumulation at any site of the brain. Hydrocephaly can be classified according to the duration of development into three groups, which are acute, subacute, and chronic hydrocephaly. Another classification of hydrocephaly is the disorder into high-pressure and normal-pressure hydrocephaly (NPH) [1–5].

2. Medical treatment options

Cerebrospinal fluid shunting is the standard treatment for hydrocephaly, but there are certain medical treatment approaches alternatively applied alone or in combination with shunting.

Treatment of hydrocephaly depends on its cause. Medical treatment is used to delay surgical procedures in hydrocephaly. Medical treatment is not effective in long-term treatment of chronic hydrocephaly but can be resumed to balance CSF dynamics (production or absorption) during this interim period. Medications include decreasing CSF secretion by the choroid plexus (acetazolamide), increasing CSF reabsorption (isosorbide, furosemide), or osmotic diuretics which increase water excretion and are used to reduce intracranial pressure (**Table 1**) [1, 2].

2.1. Reducing cerebrospinal fluid production

2.1.1. Carbonic anhydrase inhibitors

Carbonic anhydrases are a family of metalloenzymes present in the renal cortex, gastric mucosa, pancreas, liver, lungs, ciliary body, and brain, which catalyze the reversible hydration of carbon dioxide and bicarbonate. Thus, this allows to regulate intra- and extracellular concentrations of CO_2, H^+, and HCO_3^- [1, 6]. These enzymes are also found in the glia and the choroid plexus which plays secretory roles in the brain. Enzyme concentration is greater than the ciliary body in the choroid plexus [1, 6].

Complete choroid plexus carbonic anhydrase inhibition reduces cerebrospinal fluid (CSF) production by 50%. Many studies have shown that inhibition of carbonic anhydrase reduces

Intervention	Indication	Outcome	Complications
Medication (furosemide, acetazolamide)	Decrease production of CSF due to increased fluid excretion	Temporary relief of increased CSF until surgical intervention is possible	No direct evidence of effectiveness versus waiting until surgical intervention is possible; potential increased risk of complications
Lumbar puncture	Remove excess CSF through the spine to reduce pressure	Temporary relief of increased CSF until surgical intervention is possible	Possible increased risk of infection from multiple perforations
Shunt placement	All classifications of hydrocephaly in which patient can undergo surgery	Relief through drainage of excess CSF	Shunt collapse, infection, shunt failure, possible need for surgical adjustment or replacement
ETV	Obstructive hydrocephaly, shunt failure	Relief through drainage of excess fluid	Occlusion of puncture site, difficulty performing procedure, infection, hemorrhage, nerve damage

CSF, cerebrospinal fluid; ETV, endoscopic third ventriculostomy [2].

Table 1. Treatment options for hydrocephaly.

cerebrospinal fluid production. In clinical practice, the most frequently used drug which inhibits carbonic anhydrase and treats hydrocephaly patients is acetazolamide (ACZ) [6–11].

2.1.1.1. Acetazolamide

Acetazolamide (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) is a sulphonamide derivative with a potent inhibitory effect on carbonic anhydrase, which was first synthesized by Roblin and Clapp in 1950 [12]. Acetazolamide has been used in the treatment of cardiac edema, glaucoma, urinary alkalinization, metabolic alkalosis, and acute mountain sickness [1, 10, 13].

Numerous experimental and clinical studies have shown reduction in CSF production after ACZ administration. Effective doses of acetazolamide, which penetrate the blood-brain barrier to reach the choroid plexus and depress CSF flow, are on the order of 20 mg/kg [2, 6, 11, 14–18]. However, there is no standard dose of acetazolamide; the starting dose is 500 mg two times daily and a maximum dose of 4 g twice daily [19]. Recommended starting dose in children is 25 mg/kg per day with a maximum dose of 100 mg/kg or 2 g per day [20]. Complete inhibition of choroid plexus reduces CSF production by 50%, which was obtained after administration of 5–20 mg/kg of ACZ [6, 11].

In some cases, despite the reduction in CSF production, ACZ treatment could not reduce intracranial pressure, on the contrary of increasing it. This unexpected effect may be due to an indirect effect of ACZ on cerebral vessels and blood flow of the cerebrum [1].

Hypersensitivity especially sulfur allergy and hepatic failure are contraindications for ACZ and also relatively contraindicated in patients with a history of renal stones [19]. An important side effect of acetazolamide is the development of hyperchloraemic metabolic acidosis with hypokalemia. Other adverse effects include dysgeusia, paresthesia, fatigue, nausea, diarrhea, and polyuria [17]. These side effects are usually dose related. For this reason monitoring of

electrolytes is suggested during acetazolamide treatment, and potassium and bicarbonate replacement therapies are required for reducing the adverse effect of ACZ [1].

In expert opinion, acetazolamide is the most suitable drug alone or in combination with furosemide for treatment of hydrocephaly [1].

2.1.2. Furosemide

Furosemide selectively inhibits sodium reabsorption in the nephron at the loop of Henle, which is a potent loop diuretic used to treat high blood pressure, congestive heart failure, and swelling due to excess body water and also used in hyperkalemia and acute renal failure [1, 10]. Studies have shown that furosemide reduces the production of cerebrospinal fluid by inhibiting the transport of Cl^- to the cerebrospinal fluid [21–24]. In the medical treatment of hydrocephaly, the usual dose of furosemide is 1 mg/kg/day divided into two doses/day [25, 26]. Adverse effects of furosemide therapy are serum electrolyte disturbances, hypotension, and ototoxicity; for this reason, electrolyte levels have to be followed closely [10].

2.1.3. Combined therapy of furosemide and acetazolamide

Studies have shown that combination therapy of furosemide and acetazolamide was not effective in decreasing the frequency of shunting or death. Therefore, this therapy is not recommended [2, 26–29].

2.2. Osmotic diuretics

The proximal tubule and descending limb of Henle's loop are freely permeable to water. Osmotic diuretic agents are freely filtered at the glomerulus, undergo minimal reabsorption by the renal tubules causes water to be retained in these segments and promotes water diuresis. Four osmotic diuretics are available: glycerin, isosorbide, mannitol, and urea; mannitol is the most commonly used in clinical practice and the most extensively studied. Osmotic diuretics are used to increase water excretion and to promote prompt removal of renal toxins and also are used to reduce intracranial pressure [10, 30].

2.2.1. Isosorbide

Isosorbide (1,4:3,6-dianhydro-d-glucitol) is an osmotic agent developed for the treatment of glaucoma. It has also been shown to reduce the intracranial pressure [31, 32]. The single oral dose of isosorbide significantly reduces intraventricular pressure. Multiple studies showed the usual dose of isosorbide, which is 2–3 g/kg/day given at intervals of 6–12 h [33, 34].

Lorber et al. have studied the use of isosorbide in patients with various types of hydrocephaly; they reported that patient did not require shunt insertions after prolonged medication with isosorbide. But isosorbide did not replace than surgery and was less efficient than surgery [34–36].

Lorber concluded that isosorbide was safe in a large number of patients; adverse effects were less, and less frequent biochemical monitoring was required [34].

Only recommend isosorbide for short-term treatment of hydrocephaly with constant surveillance to prevent hypernatremic dehydration. However, osmotic agents are not preferred in the treatment of hydrocephaly at present [1, 31, 33, 37].

2.2.2. Mannitol

Mannitol is a six-carbon alcohol with a molecular weight of 182. This osmotic agent is not metabolized and is excreted by glomerular filtration, without any important tubular reabsorption or secretion. Also, mannitol induces an increase in serum osmolality and an osmotic gradient between the serum and intracranial compartment. Thus, removal of brain water causes to reduce ICP. Mannitol has been widely used to reduce intracranial and intraocular pressures because of its osmotic diuretic action and presumed antioxidant properties for many years. Mannitol is poorly absorbed from the gastrointestinal tract if administered orally; it would cause osmotic diarrhea, so it must be given parenterally [10, 38–40].

A dose of 0.25–1 g/kg (20% solution) mannitol is administered intravenously and infused over 5 min. Intracranial pressure should fall in 60–90 min [1, 10]. In most cases, after the administration of a bolus of mannitol, intracranial pressure rapidly decreases, but in some patients, it can worsen intracranial hypertension [10].

The effect of mannitol in the treatment of hydrocephaly has been reported in only a few studies. Hayden et al. showed that the administration of mannitol induces rapidly decreased ICP, but this effect lasted only 3–4 h and was followed by a rebound of ICP above baseline [41]. Ma et al. showed that mannitol and corticosteroids represent an effective treatment approach for patients with autoimmune diseases associated with hydrocephaly [42].

Mannitol produces a diuresis more than a natriuresis, and if free water losses are excessive, hypernatremia and hyperkalemia may ensue [10].

2.2.3. Glycerol

Glycerol is an oral osmotic agent, reduces intracranial pressure in adults with brain tumors, and was suggested as a possible agent for managing hydrocephaly [43]. On the contrary, uncontrolled trials did not support its use. Glycerol had no effect in premature infants with hydrocephaly and did not treat hydrocephaly in adults with metastatic brain cancer [44, 45].

2.3. Increasing CSF absorption

2.3.1. Glucocorticoids

Glucocorticoids have been used for decades in a range of neurological disorders associated with raised intracranial pressure [2]. Experimental studies have shown that glucocorticoids reduced CSF production and CSF flow [46, 47]. Glucocorticoids have also been used to reduce the fibrosis in the subarachnoid compartment [2].

In intraventricular hemorrhage (IVH) cases, the blood clot in the ventricular system can interrupt normal CSF flow. After the acute period of the subarachnoid hemorrhage and

bacterial or carcinomatous meningitis, cerebrospinal fluid absorption can be reduced. Glucocorticoids can slow this inflammatory response after these conditions. However, steroids do not inhibit fibroblast growth or collagen synthesis. Intrathecal or intravenous steroids have been used to prevent or alleviate arachnoiditis with poor results [1].

Some studies have shown that in autoimmune diseases associated with hydrocephaly glucocorticoids have been beneficial and corticosteroids should be considered as first-line treatment choice [42, 48–50].

3. Other treatment options

3.1. Prevention of inflammatory and fibrotic process

Intraventricular hemorrhage, subarachnoid hemorrhage, and infection (e.g., meningitis), which can lead to restriction of CSF, are all associated with secondary inflammation and fibrosis in the subarachnoid compartment. Although many mechanisms have been proposed to explain the pathophysiology of hydrocephaly, it has not yet been fully elucidated. Common theories: hemorrhage debris or clot obstruction of the CSF circulation of the arachnoid, subarachnoid, and arachnoid fibrosis, inflammation, apoptosis, autophagia, and oxidative stress [51–54].

3.2. Cerebrospinal fluid pathway modulation

Gliocytes play a destructive and curative role in the abundance of cytokines released when the brain is exposed to various lesions [55]. It also contributes to the inflammatory side by causing the structurally and functionally cleavage of the vegetative nervous system and glia cell which join the blood-brain barrier [53]. Inflammation of CSF and fibrosis is one of the general features of hydrocephaly and leads to a restriction in CSF flux. Conditions that may cause restriction include intraventricular hemorrhage, subarachnoid hemorrhage, or infection (e.g., meningitis), are all associated with secondary inflammation and fibrosis in the CSF tract, especially in the subarachnoid compartment. In children, intraventricular hemorrhage and bacterial meningitis are associated with meningeal fibrosis, which completely abolishes the subarachnoid space. In subarachnoid hemorrhagic adults, inflammation occurs in the arachnoid villi during the first week, and it is followed by collagen production [56]. Enzymatic resolution of intraventricular or subarachnoid blood collections, intervention in the inflammatory process, and the production of extracellular matrix molecules are the ways to reduce hydrocephaly development, and investigation is still going on.

3.3. Thrombolytic therapy

Some researchers have conducted experimental studies to investigate the efficacy of thrombolytic therapy in preventing posthemorrhagic hydrocephaly. In 1986, Pang et al. tested the efficacy of fibrinolytic (urokinase; uPA) in the treatment of hydrocephaly for the first time

and found that intraventricular administration of uPA effectively attenuated ventriculomegaly [52]. Similarly, several empirical studies have shown that intraventricular tPA administration is effective in preventing hydrocephaly after subarachnoid hemorrhage and regressing ventricular dilatation [57]. However, the development of perihematomal edema after tPA administration has increased question mark on this treatment method. Meta-analyses for the comparison of the uPA and tPA regarding the dissolution of the clot after intraventricular hemorrhage were made [58, 59]. Studies have shown that both uPA and tPA cause a decrease in ventricular volumes, but only uPA improves functional recovery significantly.

3.4. Anti-inflammatory therapy

There is a clear relationship between inflammation in the CSF tract and subsequent hydrocephaly development. Anti-inflammatory agents have been experimentally tested to prevent hydrocephaly after meningitis and posthemorrhage. There are numerous studies showing that corticosteroid therapy after acute bacterial meningitis significantly reduces hearing loss and neuroleptic sequelae, but the effects on hydrocephaly development are not fully known. Some studies have shown that the use of steroids does not change the likelihood of developing hydrocephaly or that this risk can be elevated in children [60–62].

3.5. Vasoactive drugs

Nimodipine is widely used as a calcium channel blocker for the control of hypertension. Experimental studies have shown that nimodipine reduces motor and cognitive function impairment after hydrocephaly [63]. Clinical trials showed that nimodipine is safe, but there is no definitive evidence for the effectiveness in the treatment of hydrocephaly. Magnesium, a calcium antagonist, also has a weaker protective effect [64].

3.6. Antioxidative therapy

Mechanical factors and reduced white matter blood flow into axonal and oligodendroglial damage can lead to neuropathophysiological damage [65]. Hypoxic changes in proteins of white matter glial and endothelial cells have been found in hydrocephaly by immunohistochemical detection of pimonidazole [66]. Antioxidant therapy is a potential pharmacological treatment for oxidative stress that is associated with brain damage in hydrocephaly. Dietary supplementation of antioxidants like oral coenzyme Q10 (CoQ10), ascorbic acid, glutathione, and lipoic acid in humans and animals reduces oxidative stress by decreasing lipid peroxidation [67].

3.7. Neuron vs axon protection

Neuronal damage in the cortex has been attributed to the disturbed activity of the noradrenergic and dopaminergic neuronal systems and synaptogenesis caused by hydrocephaly [68, 69]. Morphological changes in the hydrocephalic brain with ventricular dilation occur most characteristically in the white matter [70]. Periventricular axons in hydrocephalic brains may sustain the damage in some neurons. Studies on hydrocephaly demonstrated that hippocampal neurons show various secondary abnormalities due to deafferentation [71]. In the immature brain,

hydrocephaly affects developmental processes of cell genesis and myelination [68]. Potential early therapeutics are antioxidative, anti-inflammatory, antiapoptotic, and anti-excitotoxic drugs that can be used in neonatal hypoxic-ischemic brain injury. Memantine, a noncompetitive NMDA receptor antagonist, protects neurons and axons [72]. The neuronal cytoskeleton has been shown to play an important role in the maintenance of cytoplasmic morphology and axonal transport [15]. The functional effects of early shunt placement have been reported to prevent impairment of synaptogenesis and learning disability [73].

3.8. Cerebral stimulants

Bifemelane is a monoamine oxidase inhibitor used as an antidepressant and cerebral metabolic activator to normalize norepinephrine in the striatum and cerebral cortex [74]. Methylphenidate acts by blocking the dopamine and norepinephrine transporters and was administered to NPH patient at the dose of 20 mg after shunting improved cognitive performance and reduced apathy [75]. In another case reports, patients with hydrocephaly and akinetic mutism responded well to bromocriptine and ephedrine [76, 77]. An unshunted severe hydrocephaly patient with self-injurious behavior responded well to trazodone (200 mg/day) [78].

4. Conclusions

Hydrocephaly can be defined briefly as the excess formation of cerebrospinal fluid (CSF) leading to an increase in the fluid volume of ventricles and subarachnoid spaces of the brain [1, 2]. Water is distributed in four compartments within the brain: (i) the intracellular space, (ii) the interstitial space, (iii) the cerebral ventricles and subarachnoid spaces, and (iv) the cerebral blood vessels. CSF flow obstruction in hydrocephaly leads to transependymal flow of water and electrolytes from the enlarged ventricles into the interstitial space of the brain adjacent to the ventricular wall which is called hydrocephalic edema [79]. The osmotic agents in these patients increase serum osmolality by drawing fluid from the interstitial space into the capillaries and then out of the cranium to the general circulation. Currently used osmotic diuretics for the treatment of hydrocephaly include isosorbide and mannitol. Fibrin can also deposit in arachnoid villi that can block its openings which is resulted in reduced CSF absorption. This can be ameliorated by the administration of fibrinolytic agents injected directly into the CSF or ventricular system. Hydrocephaly secondary to an IVH has been managed with intraventricular fibrinolytic therapy, alone or in combination with carbonic anhydrase inhibitors. Another situation is the reduction of CSF absorption that can be present in the acute period after subarachnoid hemorrhage and bacterial or carcinomatous meningitis. Steroids can regulate the inflammatory response after inflammation, but fibroblast growth or collagen synthesis cannot be inhibited by steroids [2].

Hydrocephaly treatment can be classified as nonsurgical and surgical, which in turn can be divided into nonshunting and shunting procedures. Nonsurgical treatment includes reducing CSF formation, and the most common drugs used for this purpose are acetazolamide and furosemide. Hydrocephaly secondary to intraventricular hemorrhage (IVH) has been treated

by serial lumbar punctures [67] to maintain normal-pressure hydrocephaly. The aims of this process are to reduce protein and blood in the CSF and thereby to prevent the formation of fibrin. Nonshunting surgical options include endoscopic third ventriculostomy in CSF obstructions at, or distal to, the aqueduct and fenestration of the lamina terminals [80].

The major three mechanisms of medical treatment of patients with hydrocephaly are based on (i) reducing CSF production, (ii) decreasing brain water content, and (iii) increasing CSF. About two-thirds of CSF is formed at the choroid plexus, and the other third is formed in the brain and spinal cord [80]. After the filtration of water across the choroidal epithelium, the increased pressure of CSF then involves active transport of water and ions across the choroidal sacs which are controlled mainly by Na+/K+ ATPase. Active secretion of water and ions by the choroidal epithelium into the ventricles are controlled by the activity of carbonic anhydrase [76]. Digoxin and ouabain are effective drugs that are used as Na+/K+ ATPase inhibitors [78]. Carbonic anhydrase inhibitors are effective drugs still used to decrease the rate of CSF production in the choroid plexus. Loop diuretic agents, such as furosemide, have also been used to reduce CSF formation.

Conflict of interest

No conflict of interest was declared by the authors. The authors declared that this study had received no financial support.

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Section 5

Endoscopic Third Ventriculostomy

Chapter 6

Endoscopic Third Ventriculostomy, Indications and Challenges

Ehab Ahmed El Refaee and Ahmed A Abdullah

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73518

Abstract

Endoscopic third ventriculostomy (ETV) allows the cerebrospinal fluid (CSF) to flow directly from the third ventricle through the fashioned ventriculostoma to the interpeduncular cistern, by passing the site of obstruction. In spite of the wide variety of indications where ETV is implemented, its success rate is still debatable especially in certain age groups, where it is most successful in adult patients with obstructive hydrocephalus and it has an identifiable failure rate in children less than 6 months of age. Several factors would affect the success rate of ETV, which are related to the patient's age, pathology, and intraoperative findings. This chapter covers most of the current debates considering ETV.

Keywords: endoscopic third ventriculostomy, obstructive hydrocephalus, choroid plexus coagulation

1. Introduction

In spite of the ongoing advances, endoscopic third ventriculostomy (ETV) remains one of the eminent developments in the history of neurosurgery. It allows the cerebrospinal fluid (CSF) to flow directly from the third ventricle through the fashioned ventriculostoma to the interpeduncular cistern, bypassing the aqueduct and the CSF pathways related to the fourth ventricle and the posterior fossa. The idea of internal visualization of the ventricular system via performing surgery through a small hole in the skull was the initiative for the development of ETV. During the last decades, ETV ran with the advances in visual and optical technologies and made an extraordinary benefit of them.

The first ever use of an optical tool to visualize the interior of the human body was performed by Bozzini in 1806 [1]. A hundred years later, Lespinasse used a cystoscope to visualize the ventricles of two hydrocephalic children [2]. In 1918, Dandy performed an endoscopic avulsion of the choroid plexus in five hydrocephalic children (where four died) [3]; he called his instrument a "ventriculoscope." In 1922, he opened the floor of the third ventricle by sacrificing an optic nerve [3, 4]. In 1923, Mixter performed a third ventriculocisternostomy through the anterior fontanelle [5], which is considered the first ever successful ETV. In 1947, McNickle was the first to introduce a percutaneous method of performing the third ventriculostomy that led to decline of the complication rate, thus improving the success rate [6]. Afterward the endoscopic technique progressively developed to reach the current modifications in the ventriculoscope for better, clear, and safe visualization of the intraventricular anatomical structures [7].

There is still a detectable failure rate of all treatment modalities of hydrocephalus. However, ETV represents a convenient and easy mode of management. In the recent studies that evaluated the endoscopic third ventriculostomies performed for the treatment of obstructive hydrocephalus, success rates were found between 50 and 94% [8–11]. The type of hydrocephalus and age of the patient, in addition to the surgical technique, play an important role in the success of the ETV [11]. We will discuss comprehensively the surgical technique, indications, and current challenges regarding the increase of the success rate of the ETV.

2. Endoscopic anatomy

A preoperative MRI is almost always needed prior to surgery. From the frontal coronal burr hole, one reaches first the central part of the lateral ventricle near the frontal horn. The frontal horn is demarcated by the absence of choroid plexus. The lateral wall is formed by the nucleus with subependymal veins; medially is the septum pellucidum with septal veins. The choroid plexus and the foramen of Monro are very important landmarks for the central part of the lateral ventricle. The plexus is situated in the floor of the lateral ventricle, the thalamostriate vein lies laterally, and the septal vein's meeting point is on the medial wall; these three structures form the Y-shaped configuration necessary for orientation. The foramen of Monro is formed anterolaterally by the fornix, posteromedially by the anterior thalamic tubercle (**Figure 1**). On looking backwards with the endoscope, the body of the lateral ventricle back to the region of the trigone, with the body of the caudate laterally underlying the thalamostriate vein and the stria terminalis thalami. Adequate orientation of the morbid anatomy that can occur due to chronic hydrocephalus is needed [12–14].

By entering the foramen of Monro, the floor of the anterior part of the third ventricle is clearly identifiable, with the mammillary bodies and tuber cinereum as the two main structures needed for the anatomical orientation (**Figure 1**) [14].

Liliequist's membrane is an arachnoid leaflet situated in the basal cisterns and is a very important anatomical structure in the postsellar region.

http://dx.doi.org/10.5772/intechopen.73518

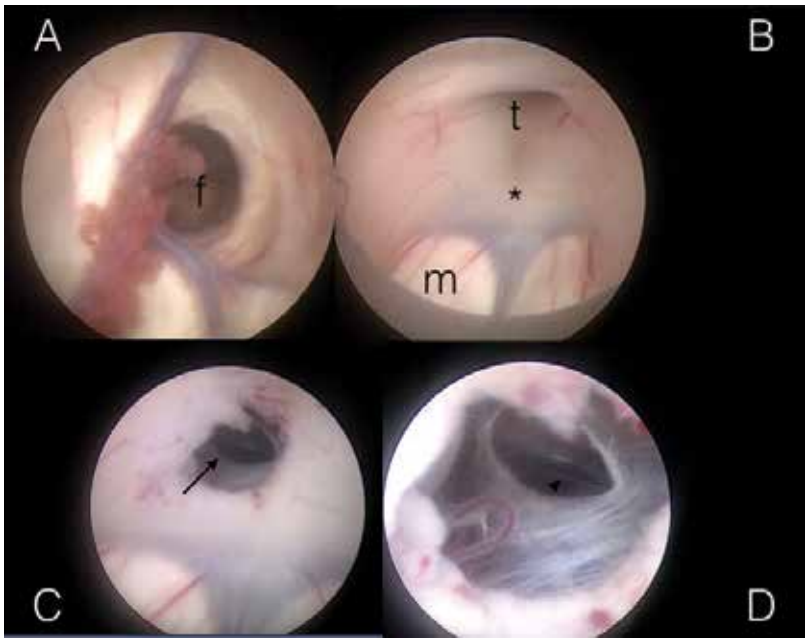

Figure 1. (A) Endoscopic view of the foramen of Monro (f) and its boundaries. (B) Endoscopic view of the floor of the third ventricle before perforation for ETV showing the planned site of perforation (asterisk) in between the tuber cinereum (t) and the mammillary bodies (m). (C) Endoscopic visualization of the membrane of Liliequist after perforation (arrow). (D) Endoscopic visualization of the basilar artery after opening the membrane of Liliequist (arrowhead).

3. Indications

ETV is considered the first management option in adult patients with obstructive hydrocephalus by many neurosurgeons. It is a reliable management option in adults with aqueductal stenosis with a success rate that reach 88% [15]. Stenosis at the aqueduct of Sylvius can be congenital or acquired. In three quarters of cases, the root cause might be unknown [16]. It is not considered as a stable condition as it can be tolerated for years, where stenosis is aggravated by trauma, subarachnoid hemorrhage, viral infection, or gradual accumulation of the CSF proximal to the aqueduct in partial obstruction [16–18]. In a previous study, clinical improvement with identifiable success of the procedure was detected in 86.4% of cases [19], where the success rate was lower in secondary ETV after VP shunt (**Figure 2**). This would be better identified in patients with previous history of multiple VP shunt revisions where the ETV failure is relatively more encountered [19, 20]. ETV is also preferred as the first-line management of hydrocephalus due to obstruction of the aqueduct of Sylvius with pineal tumors or tectal gliomas [21–23].

ETV is less successful in pediatric age groups, with the lowest success rate in children younger than 6 months of age, even in aqueductal stenosis [24, 25].

The application of the ETV has been expanded to patients with hydrocephalus associated with fourth ventricular outlet obstruction, Dandy-Walker malformation [26], Chiari malformation [27–29], communicating hydrocephalus [30], and normal pressure hydrocephalus [31, 32].

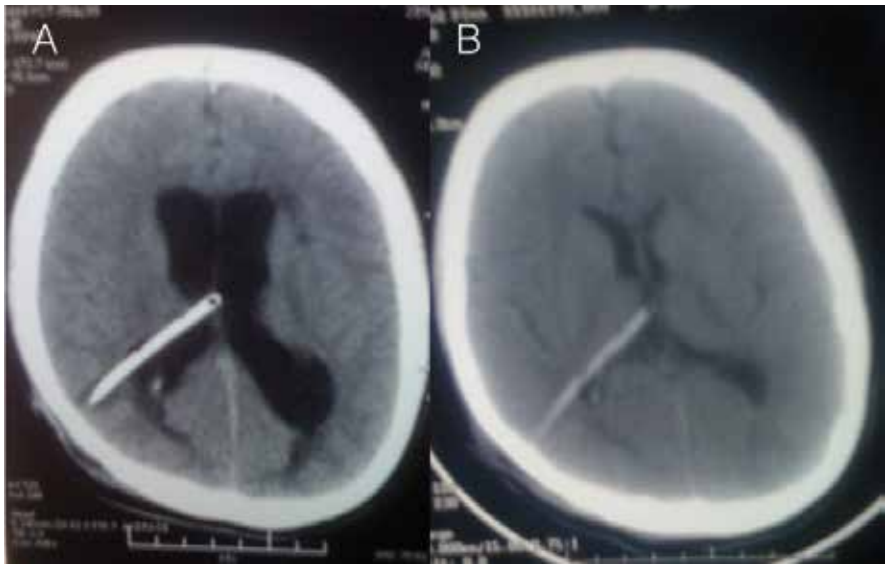

Figure 2. CT of the brain of a previously shunted 12-year-old male with aqueductal stenosis that had signs of increased tension and VP shunt failure; the CT shows enlarged ventricles (A) where ETV was performed without removing the shunt. Follow-up CT of the brain 3 months afterward showed decline in the ventricular size (B) which was accompanied by clinical improvement of the patient.

However, in exclusion to adult-type obstructive hydrocephalus, there is still a lack of strong evidence that supports the procedure.

4. Surgical technique

Under general anesthesia, the patient is restrained, disinfected, and draped as for a frontal burr hole; after opening the dura, a small corticectomy is performed, and a blunt obturator cannula is inserted, with free hands, directed medially toward the ipsilateral medial epicanthus and posteriorly toward the tragus of the ear. After insuring being in the ventricles by the outflow of CSF, the optical visualization system is inserted; we use the Lotta endoscope (Karl Storz, Tuttlingen, Germany) [7].

The first structure identified is the foramen of Monro, with the choroid plexus attached to the posterior margin (**Figure 1A**). The endoscope is introduced through the foramen to the third ventricle, and the floor is identified (**Figure 1B**). A small puncture is done using the decq forceps as posterior as possible to the infundibular recess and avoiding the mammillary bodies and the small arterioles running in this area. The endoscope is then advanced near to the puncture to visualize Liliequist's membrane which must be opened, after which, the CSF flow should be clearly visualized through the opening (**Figure 1C,D**).

It is important to clearly visualize the fornix before introducing the endoscope to the third ventricle. Opening the floor of the third ventricle with ballooning the fenestra aiming for its

widening, with subsequent opening of the liliquist membrane, is important for a direct visualization of a naked basilar artery (BA) [25]. A delicate surgical technique is required with experienced hands during the opening of the floor of the third ventricle till the BA is clearly visualized to avoid major vascular injury [33].

5. Outcome

5.1. Clinical evaluation and radiological evaluation

The ETV Success Score (ETVSS) has been developed and validated to predict ETV success based on certain variables [34, 35]. It depends on predicting the success according to the age of the patient, cause of hydrocephalus, and presence of the previous shunt operation. The success rate can be predicted according to these variables. However, intraoperative factors "like the presence of excessive adhesions, mobility of the stoma, excessive bleeding, and opening of Liliequist's membrane" (**Figure 3**) should be taken into consideration in predicting the success of ETV [36]. In addition, the VP shunt independence is considered a generalized but competent method to measure the success of ETV after VP shunt failure [37, 38].

The change of the ventricular size with a deterioration of the clinical condition has been well known as one of the signs that identify hydrocephalus. In addition, the decrease of the ventricular size after management which accompanied improvement of the general condition has its additional value of success confirmation (**Figure 2**). However, the change of the ventricular size is not well supported as an accurate measurement of the effective treatment of hydrocephalus, especially when it is irrelevant to the clinical condition of the patient [39].

Specific intraoperative factors are considered significant in addition to the associated morbidity. This would include the duration of surgery, type(s) of endoscope used, and degree of intraoperative bleeding [33, 36].

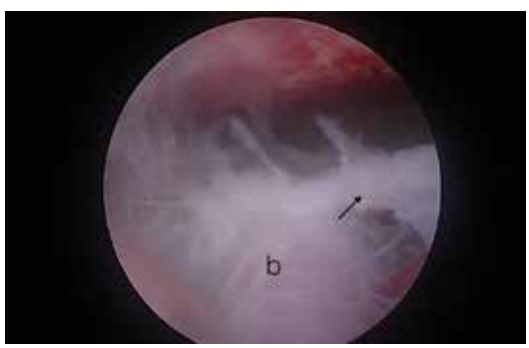

Figure 3. Another patient during ETV where thick arachnoid membranes (arrow) surrounding the basilar artery (b) denoting possibility of ETV failure.

6. Challenges and complications

ETV is considered a safe and direct procedure by a huge group of neurosurgeons, and on the contrary due to the low incidence of mortality due to vascular injury, a fatal risk in comparison to VP shunt implantation is considered by another group of neurosurgeons [33]. Insertion of a foreign hardware to the human's body is always associated with increased risk of infection and/or hardware malfunction, which favors the trial of the ETV as a primary management modality especially in adult patients with obstructive hydrocephalus [15]. On the contrary, late failure or reclosure is considered as a potential risk that can be fatal after ETV [40].

The success of the secondary ETV after ventricular shunt insertion is still debatable, where some studies identified the previous shunting procedure as a weakening factor against the ETV success [19, 41]. Other studies mentioned the success of the secondary ETV in hindering the shunt dependency [42, 43]. In our opinion, ETV is considered a competent treatment option in cases with obstructive hydrocephalus with repeated VP shunt failure. It can be easily tried and may lead to shunt independency.

Seven to ten percent of patients with Chiari type I present with hydrocephalus [44–46]. ETV has proven to be highly effective in the treatment of obstructive hydrocephalus, thus explaining its increasing use in cases of Chiari I-associated hydrocephalus [27, 47–50] with some limitations. The literature shows that most of patients may benefit from ETV. Syringomyelia shows better improvement than CIM. This is most probably due to the obvious role of hydrocephalus and increased pressure in the development of syrinx.

The large incidence of ETV failure in children leads to increased rate of shunt dependency in pediatric age groups, even in obstructive hydrocephalus [24]. The drop of the number of children where ETV is successful is thought due to the rapid formation of the arachnoid and scar membranes in children which closed the ventriculostoma rapidly [51]. On the contrary some authors support the ETV as effective management of obstructive hydrocephalus even in young children [52]. Other authors report the clear impact of age on the success rate of ETV when talking about infants, where the success rate increases gradually during the first months of life. Many studies were performed to determine the cause of failure in young children thus poor absorption of CSF and closure of the ventriculostoma or formation of new arachnoid membranes in the basal cisterns [51, 53]. In addition, reduced absorption of CSF as a cause of failure of ETV was recognized by many authors [54, 55] to be related to poor absorption from the arachnoid villi in young children and to the high compliance of the newborn skull in relation to older children leading to less CSF pressure gradient across the arachnoid villi, added to the previously mentioned probable failure due to arachnoid scarring (**Figure 3**) [56]. This was the initiative to relaunch the choroid plexus coagulation (CPC) technique to decrease the CSF production: thus, it would increase the success of ETV when performed together.

Due to repeated reports about failure in patients below 2 years old [57–59], a consideration of not doing this procedure in this age group has been implemented; however, it is now widely accepted that the etiology of the hydrocephalus rather than the age of the patient is more important in determining the efficacy of ETV even in patients less than 2 years old [60]. ETV

has been shown to be less effective in patients with myelomeningocele and intraventricular hemorrhage, while having a similar success rate to adults in cases of aqueductal stenosis [60].

6.1. Choroid plexus coagulation

Choroid plexus coagulation is the surgical ablation of the choroid plexus either endoscopic or microscopic [61]. It has recently become popular as a method of management of hydrocephalus not caused by the overproduction of CSF [62–65].

Since 2005, the combination of CPC and ETV became more popular but ever since remained a debatable issue [66]. Warf and colleagues published their results of ETV + CPC in 2005; the majority of patients were infants. The long-term outcome and neurocognitive results were reported in later studies and showed that ETV + CPC increased the success rate from 20 to 47% to 63 to 76%. In North American experience, multicentric studies proved the safety of combined ETV/CPC procedure with technical improvement [67–69].

In 2004, Morota described the technique of CPC through a parietal burr hole using a flexible endoscope and monopolar cautery [70]. Warf described the combined ETV/CPC procedure using the flexible endoscope, through a frontal burr hole. Bilateral CPC adds 15–30 minutes to the procedure; adequate coagulation is realized by the blanching of all visible parts of the choroid plexus and the associated blood vessels [61, 66, 67]. The overall mortality (within 30 days of the surgery) was 1.3%. There was no increase in mortality compared to those with ETV alone and those with ETV + CPC [61, 66].

6.2. Communicating hydrocephalus

Patients with postinfectious and posthemorrhagic hydrocephalus have not been included in ETV studies in significant numbers. Instead, such patients are considered by many authors to be prone to failure of ventriculostomy, thus contraindicating ETV [48, 71, 72].

Posthemorrhagic hydrocephalus of prematurity (PHHP) is one of the most common causes of infant hydrocephalus in developed countries; this is mainly due to the high standards of care for prematurely born babies [73].

PHHP occurs when blood in the CSF-filled spaces, together with the initial inflammatory reaction in the ependyma, would lead to obstruction of CSF outflow and hinder absorption, usually by the mechanism of posterior fossa arachnoiditis and aqueductal obstruction. In addition, a diffuse inflammatory reaction in the basal cisterns could coexist, which supports the theory that predict the ETV failure in these cases [73, 74].

On the contrary, putting these in consideration, with the fact that the use of VP shunts in these too young patients carries a high risk of failure, makes trial for an ETV a possible choice for treating this group of patients, and decreasing shunt dependency [73].

A large multicentric retrospective study showed that patients with obstructive hydrocephalus and history of hemorrhage or infection may be candidates for ETV. In this group ETV is reasonably safe, with a success rate that is comparable to the general series. ETV is highly

successful when performed in patients with intraventricular hemorrhage (IVH) and previous shunting; it is also highly successful in patients with primary aqueductal stenosis, while patients with history of both hemorrhage and infection are poor candidates for ETV [72, 73].

Some authors recommended the use of temporary CSF diversion, such as Ommaya reservoir in the acute stage of IVH, and performed the ETV when evidence of ventricular dilatation is obvious [75]. Moreover, in adult patients with IVH, studies showed that endoscopic third ventriculostomy may be an option in cases of acute intracranial hemorrhage with intraventricular extension in which there is clearly established CSF outflow obstruction, with special concern paid toward the surgeon experience [76].

6.3. Redo success rate

The question of in which cases a reclosure of the ETV opening occurs is still not answered. The recent data indicate that failure of ETV may occur immediately after the primary procedure, where the main cause is poor indication of remaining membranes or even years after where it is due to scarring [77, 78]. A redo ETV is supported before deciding to do other CSF diversion procedures whenever a failure was encountered, at which the ETVSS predicts the chance of successful redo ETV. Failure of the ETV and thus redo ETV can be also predicted by the presence of excessive prepontine arachnoid membranes in addition the use of external ventricular drain EVD [78, 79].

6.4. Dandy-Walker malformation

In such cases, hydrocephalus is caused by a large posterior fossa cyst in cases of Dandy-Walker malformation. ETV alone, with aqueductal stent, or with fenestration of the cyst can be sufficient in some cases to control hydrocephalus [80, 81].

Cystoventricular stent placement with endoscopic third ventriculostomy is a promising alternative in patients with Dandy-Walker malformation with aqueductal obstruction [26].

6.5. Normal pressure hydrocephalus

ETV has been recently introduced as a treatment option for normal pressure hydrocephalus. Gangemi et al. mentioned an overall success rate of 72%, in a series of 25 patients [31]. In a larger multicentric study, the clinical improvement reached 69.1%, where the improvement was correlated to the short clinical history, better neurological score before the operation, and the intraoperative appearance of normal cerebral pulsations [82]. Hailong et al. reported an 82.35% success rate and claimed that the preoperative Kiefer score and the patient's age are significant prognostic factors for ETV dysfunction [30]. However, the criteria of patients' selection and the small sample size in most previous literature would justify the actual deficiency of solid evidence that supports ETV as a treatment option in normal pressure hydrocephalus. Large-scale clinical studies are needed to reach better evidence and define the role of ETV in the management of INPH [83].

7. Complications

In a previous literature review, the overall complication rate was 8.5%; among the individual series, the rate ranged from 0 to 31.2%. Complications reported in the immediate postoperative period were mainly hemorrhagic, infectious, subdural collections and CSF leak [84]. These complications represent actually the same complications that can be encountered with the ventricular shunting in exclusion of the hardware-related complications with variable incidence rates that can differ according to the variable age groups.

In conclusion, although ETV is considered a reliable resort to control the hydrocephalus without implanting a shunt, the debate on its success rate is still not finalized especially in young children and communicating hydrocephalus. So that more studies covering those types are warranted.

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Chapter 7

Endoscopic Third Ventriculostomy

Tugrul Cem Unal and Aydin Aydoseli

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75394

Abstract

Endoscopic third ventriculostomy (ETV) is a minimally invasive procedure commonly used to treat obstructive hydrocephalus. The objectives of the procedure are to fenestrate the floor of the third ventricle using a neuroendoscopic approach and to provide a cerebrospinal fluid (CSF) diversion. With high success rates published over the years, ETV became a routine modality for the obstructive hydrocephalus treatment. Furthermore, indications for ETV are expanding day by day and are no longer limited to obstructive hydrocephalus. Endoscopic third ventriculostomy has lower complication rate and has significant advantages compared to other CSF diversion techniques. Efficiency and safety of ETV are increasing with the advancements in technology.

Keywords: neuroendoscopy, hydrocephalus, endoscopic third ventriculostomy

1. Introduction

In the past decades, endoscopic third ventriculostomy (ETV) became a novel procedure for the treatment of obstructive hydrocephalus of various etiologies including aqueductal stenosis and tumors obstructing cerebrospinal fluid (CSF) pathways. As experience in this field grows, the indications for ETV are expanding to meningomyelocele, Chiari malformation, or Dandy-Walker-related hydrocephalus cases or even to noncommunicating types of hydrocephalus. In select cases, ETV is becoming more and more preferable to ventriculoperitoneal (VP) shunt placement due to avoidance of shunt dependency and complications that come with the shunting [1]. Like indications, the technique for ETV is also refining gradually. Efficiency and safety of the procedure increase day by day with the advancements of tools, neuroimaging, and stereotactic technologies.

2. History

Walter Dandy is considered by many the father of neuroendoscopy. He described an endoscopic approach to choroid plexectomy for treatment of hydrocephalus [2]. Dandy also performed a fenestration in lamina terminalis via craniotomy in 1922, pioneering the concept of ventriculostomy, although the first successful endoscopic ventriculostomy is attributed to William Mixter. In 1923 Mixter performed a ventriculography combined with ventriculostomy using an ureteroscope in a 9-year-old girl with noncommunicating hydrocephalus [3]. Tracy Putnam and John Scarff, respectively, designed endoscopes suitable for ventricular surgery [4, 5]. Scarff made several modifications to the design like angled view, continuous irrigation system for replacing the CSF, a mobile unipolar electrode [5, 6].

CSF diversion techniques became widely popular starting the 1950s [7]. The high rate of mortality and morbidity in endoscopic techniques with the technical difficulties led the shunt operations taking place in this era. However, even with the advancements in the shunt technology, CSF diversion was never perfect and had its own rate of complications like infection and dysfunction. After the introduction of shunting systems in the 1950s, ETV lost its popularity but only to regain in the 1970s and 1980s. Starting at the end of the 1970s, an interest in minimally invasive surgery emerged with the advancements in neuroimaging, stereotaxis, lighting, and computer technology [7]. Since then, endoscopic third ventriculostomy became a routine modality for the treatment of obstructive hydrocephalus with many other indications.

3. Operative technique

3.1. Important landmarks

Recognition of critical landmarks and structures in the ventricles is very important to achieve a successful ETV. The choroid plexus is an important anatomical landmark in the lateral ventricle as its anterior part extends to the foramen of Monro and then to the third ventricle (**Figure 1**). Recognizing the choroid plexus in the lateral ventricle gives the surgeon a road map to the third ventricle. Even with gross distortions in the ventricular anatomy, the choroid plexus remains at choroidal fissure and gives the surgeon an important navigational tool. Another important anatomical landmark is the fornix, which forms the superior and anterior margin of the foramen of Monro. Because of its location, the fornix is prone to injury when endoscope advancement is made from lateral to the third ventricle. The risk of injury increases with multiple passages. The thalamostriate vein is also an important landmark when recognized, as it dives to the foramen of Monro with the choroid plexus (**Figure 1**).

Hypothalamus forms the lateral walls of the third ventricle. The supraoptic and paraventricular arcuate nuclei are the structures most prone to injury during an ETV because of the localization in the lateral wall and proximity to the trajectory. Injury to these structures may result in severe endocrinologic disturbances as vasopressin and oxytocin are produced in these nuclei [8].

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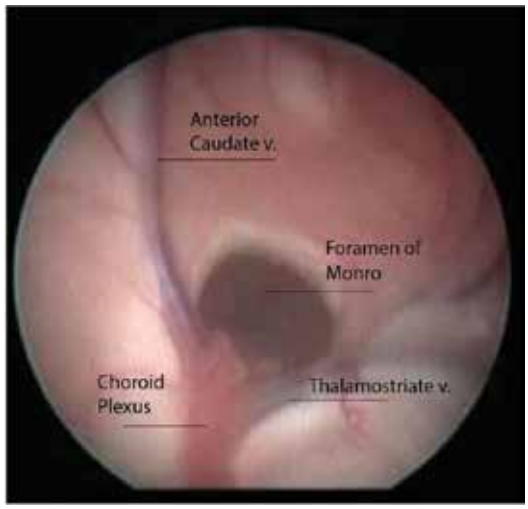

Figure 1. Endoscopic view of the foramen of Monro and adjacent structures.

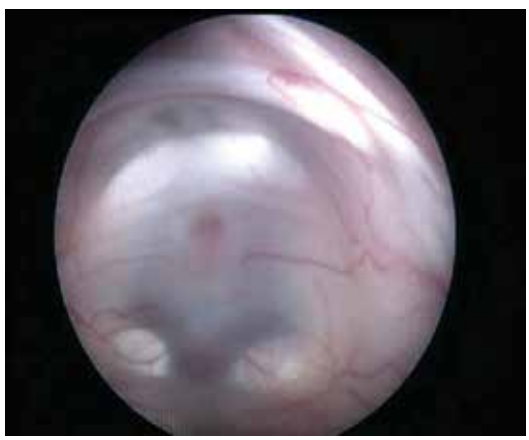

Figure 2. Endoscopic view of the floor of the third ventricle.

The third ventricular floor is essentially a thin portion of the hypothalamus between two parts of it located in the lateral walls of the third ventricle. The limits to the floor are mammillary bodies posteriorly, the walls of the third ventricle laterally, and infundibular recess anteriorly. The third ventricle perforation is generally made in a safe zone accepted in just anterior of the midway between the infundibular recess and mammillary bodies (**Figure 2**). If penetrated more posterior to this point, one may encounter the basilar tip and anteriorly clivus.

3.2. Endoscope

Basically, there are three types of endoscopes: rigid, semirigid, and flexible. In terms of optic systems available, neuroendoscopes are currently rod-lens and fiber-optic [9]. Different types of

endoscopes might be optimal for treatment of different types of disease. The choice of the endoscope must be made considering separate pathologies and the anatomical variations. Visibility, adaptability, and invasiveness of endoscopes vary from type to type; thus, neuroendoscopist must be flexible choosing the endoscope system with consideration of different diseases [10].

3.3. Approach

Since the introduction of ETV, many operative techniques have been proposed [11–14]. The main approach to the floor of the third ventricle stays consistent; surgical trajectory is from a frontal burr-hole to the lateral ventricle and foramen of Monro (**Figure 3**) [10]. Anatomical considerations are very important for the success of the procedure. Many authors have studied the endoscopic anatomy of ventricular system [15–17]. Distortion of the ventricles by hydrocephalus can lead to anatomical variations like persistence of the infundibular recess and empty sella. Successful perforation of the ventricular floor is thought to be correlated to the absence of these variations. Neuronavigation and preoperative advanced neuroimaging are powerful tools for understanding these variations and taking precaution for increasing the success rate of the procedure.

The trajectory is almost standard for a typical hydrocephalus patient with enlarged ventricles undergoing ETV for the first time. This trajectory consists of an entry point slightly anterior to the coronal suture and slightly lateral to the midpupillary line. The authors recommend an entry point 3 cm lateral to the midline and 1 cm anterior to the coronal suture. The orientation of the endoscope should be slightly medial and in line with eternal acoustic meatus in the anterior–posterior direction. This approach that has a trajectory is optimal in a patient with

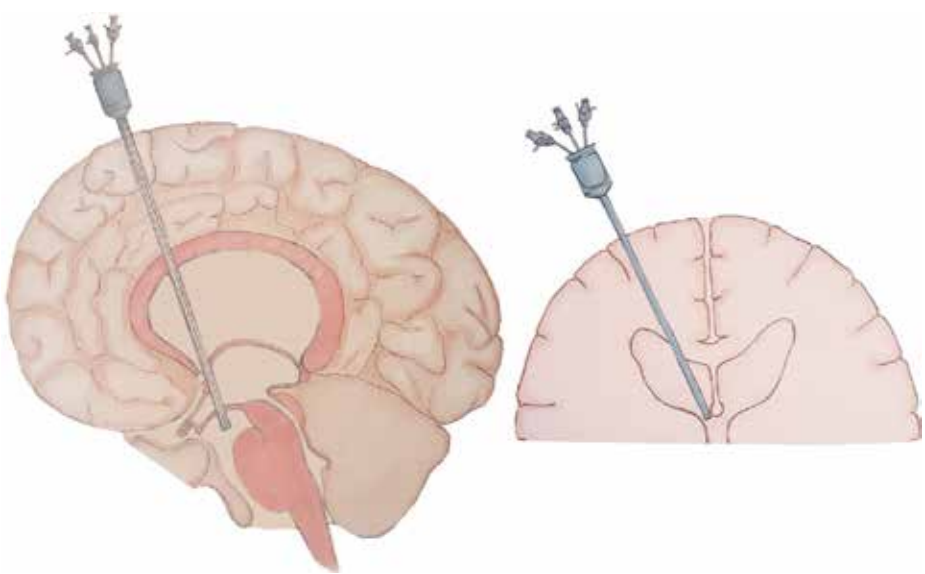

Figure 3. Trajectory of the endoscope for the third ventriculostomy.

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enlarged ventricles for entering the lateral ventricle, passing the foramen of Monro and reaching the floor of the third ventricle.

In previously operated patients for a shunt with the use of Kocher's point, the existing burrhole might not be ideal because it will be located more anteriorly. In this situation, a new burrhole and sometimes a new incision are often recommended for an optimal and safe approach to the third ventricle floor. The orientation of the trajectory still could be changed considering the ventricle size and shape. Examining radiographic features beforehand is always crucial—especially coronal and sagittal sections—and may cause slight changes to the approach. The entry point might be slightly medial in case of ventricles not obviously dilated, for example.

As the stereotactic and neuronavigation system advance, application of these systems became available for ETV [18, 19]. These systems provide planning and executing a precise trajectory for a safe procedure (**Figure 4**). Other than trajectory planning, these systems help the surgeon accurately puncture the safe zone in the floor of the ventricle preventing gross complications as basilar artery or hypothalamic injury. Doppler ultrasound can be applied to ETV with a microprobe for localization of the basilar artery preventing injury [7].

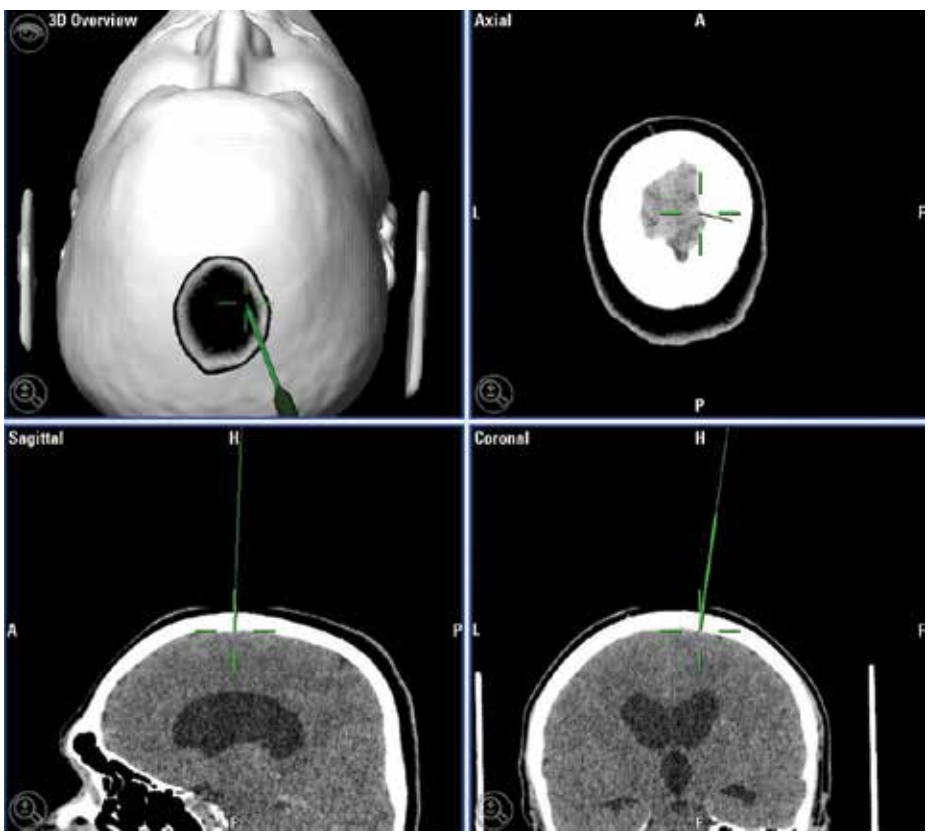

Figure 4. Trajectory planning with neuronavigation software.

3.4. Fenestration techniques

Balloon dilatation technique is the most widespread technique used for ventriculostomy [10, 20, 21]. In this technique, surgeon opens the floor using a blunt dissector or a blunt monopolar coagulator tip through the working channel of the endoscope. Then, the dissector is drawn, and a Fogarty three-French balloon catheter (might be two-French depending on the working channel diameter of the endoscope) or a specialized NeuroBalloon catheter with two balloon compartments is passed through the initial fenestration. The balloon is slowly inflated inside the fenestration to enlarge the opening (**Figure 5**). Next, the balloon is deflated and pulled back. There are many advantages with this technique: the procedure can be repeated many times safely, the floor of the ventricle and even the prepontine cistern are

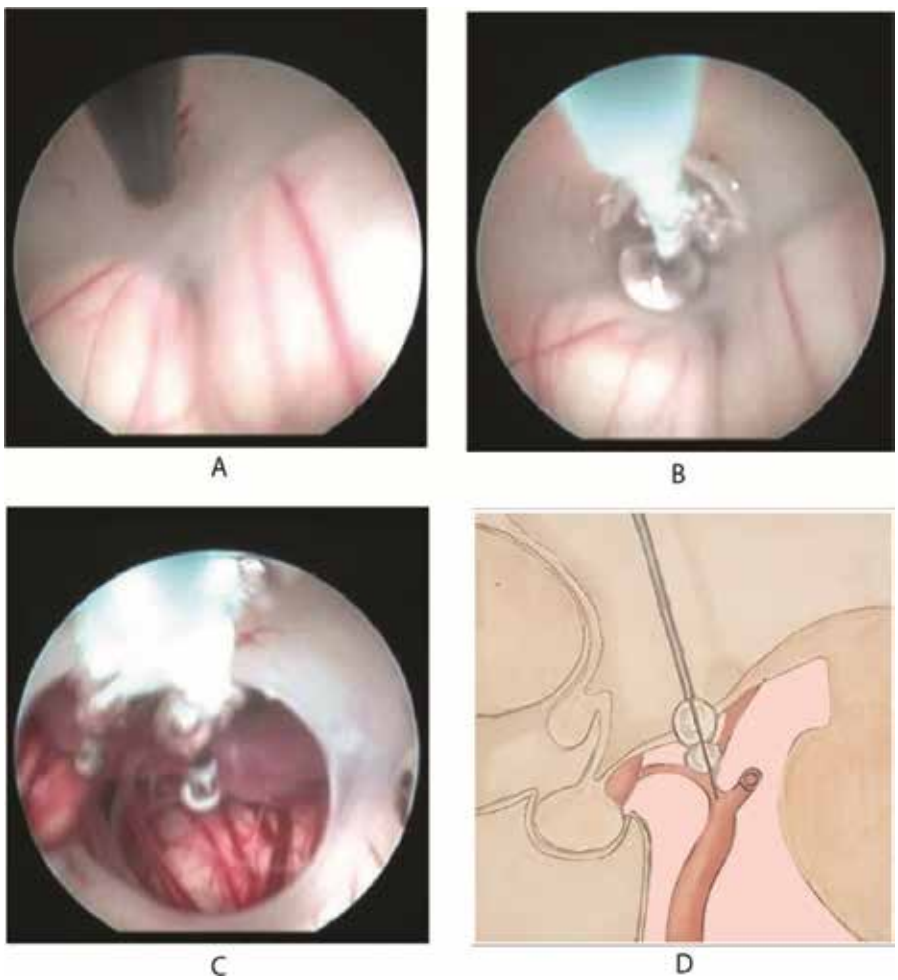

Figure 5. Endoscopic third ventriculostomy using balloon dilatation. The floor of the third ventricle is perforated with a blunt cautery tip (A), and the NeuroBalloon is passed through the hole and inflated (B). The structures in the prepontine cistern are visible through the fully inflated balloon (C, D).

visualized during wthewinflation, and balloon inflation can be used as a hemostatic tool in the event of capillary bleeding from the floor. The advancement of the endoscope after fenestration is recommended for visualization of arachnoid strips and Liliequist membrane [10]. These advantages make balloon dilatation the safest technique for fenestration.

A variation of techniques can be used for puncturing the floor of the third ventricle. Perhaps, the most basic technique is performing the fenestration via the tip of the endoscope. Multiple series showed the efficiency of this technique [6, 19]. However, some drawbacks exist for this approach. The endoscope should be small in diameter, vision is obscured during dissection of the floor, and a steep learning curve is present. Many other techniques exist like saline torch and laser energy; however, the safety and efficiency of these techniques are questionable [22].

4. Indications

The most common indication for ETV is obstructive hydrocephalus caused by primary aqueductal stenosis. Various authors published many series demonstrating the effectiveness of ETV in aqueductal stenosis patients. The success rate in aqueductal stenosis is reported up to 90%. Thus, ETV is established almost universally as treatment of choice for aqueductal stenosis [6, 23, 24].

Many other obstructive pathologies can be treated with ETV. Although shunting is a treatment option, hydrocephalus caused by lateral ventricle entrapment can be adequately treated with endoscopic septal fenestration combined with ETV [25]. In case of the isolated fourth ventricle, aqueductoplasty with endoscopic approach presents a safe and effective method [26]. This approach seems to be less invasive than microsurgical fenestration and more reliable than the fourth ventricle shunts. Endoscopic third ventriculostomy proved to be effective in the fourth ventricle outlet obstruction without Chiari malformation or visible obstructive mass [27]. These idiopathic stenosis cases are treated successfully with ETV even resolving accompanying pathologies like syringomyelia. Dandy-Walker malformation can also be treated with ETV and a stent between the third ventricle and posterior fossa when accompanied by aqueductal stenosis [28–30]. In complex obstructive syndromes, neuroendoscopy and ETV are frequently used by neurosurgeons.

In case of acute intraventricular hemorrhages, ETV can be used as a replacement for external ventricular drainage. In supratentorial intraventricular hemorrhages, ETV is shown to be useful for relieving acute hydrocephalus in addition to clot aspiration [31]. Although the use of the ETV for supratentorial hemorrhages is controversial, in posterior fossa hemorrhages, ETV is proven to be very effective for the treatment of acute hydrocephalus [32]. In case of obstruction caused by the fourth ventricular or cerebellar hematomas, ETV seems to be an effective and a safe alternative to external ventricular drainage.

Neuroendoscopy offers the possibility to combine ETV and tumor biopsy in selected intraventricular and paraventricular tumors [33–36]. Developing technologies like endoscopic ultrasonic aspirator makes total removal of the tumors possible. Endoscopic third ventriculostomy is even possible for tumors located in the third ventricle floor without any morbidity [37]. Although ETV is an effective treatment for relief of hydrocephalus in intraventricular tumors,

neuroendoscopic approach presents a difficulty when the anatomical landmarks are distorted by the growth of the tumor.

Tectal and pineal tumors presenting with acute hydrocephalus also present an indication for tumor biopsy and ETV [38]. The management of these tumors depending on histology is combined open surgery and radiotherapy or chemotherapy. In the presence of obstructive hydrocephalus, neuroendoscopy presents an opportunity for the long term relieving the hydrocephalus and adequate tumor biopsy for determining the management. Long-term control of hydrocephalus is possible with ETV in tectal plate tumors [39].

In posterior fossa tumors, preoperative hydrocephalus can be managed with external ventricular drainage as well as ETV [40–42]. Postoperative hydrocephalus in posterior fossa tumors presents a major problem in these patients. In posterior fossa tumors, about 36% of patients need a CSF diversion surgery postoperatively [43]. The outcomes of ETV in postoperative hydrocephalus are about as good as shunting; however, failure happens earlier than VP shunts [44]. It is proven that ETV performed prior to surgery reduces significantly the incidence of postoperative hydrocephalus although it does not prevent hydrocephalus in all cases. It does however prevent acute postoperative hydrocephalus due to cerebellar swelling and presents a cleaner and more physiologic method compared to external ventricular drainage [41]. The effectiveness of ETV is also demonstrated in brain stem gliomas causing hydrocephalus [45].

The treatment of choice for suprasellar arachnoid cysts is endoscopic fenestration of the cyst into ventricular system combined with ETV (cystoventriculocisternostomy). Several series demonstrated cyst and hydrocephalus regression with this technique [46, 47]. Cystostomy and ETV might also be indicated in some pineal cysts and quadrigeminal cysts presented with hydrocephalus [48, 49].

Contrary to obstructive hydrocephalus, indications of communicating hydrocephalus are controversial [50]. There are successful series of ETV on normal pressure hydrocephalus in literature with improvement rate after ETV up to 69% [51]. However, the etiology of this success is not yet well defined. Some authors argue that the third ventriculostomy relieves periventricular tissue stress improving the perfusion [52].

In patients with Chiari malformation type I with concomitant hydrocephalus, ETV is proven to be beneficial [53]. In these patients relief of symptoms, ascent of the tonsils, regression of hydrocephalus, and syringomyelia are seen after ETV [54, 55]. The established treatment for these patients is suboccipital craniectomy and duraplasty combined with CSF diversion surgery. In these selected cases, ETV proves to be successful meaning that the cure might be achieved in a less invasive and less complicated manner. As for Chiari malformation type II, the overall success for patients with concomitant meningomyelocele and hydrocephalus is up to 72% [56]. In these patients, ETV presents a safe and an effective way to deal with hydrocephalus and long-term shunt independence [57].

5. Outcomes

Success rates of EVT vary from 50–90% in literature [52, 58]. Good outcomes are highest with up to about 90% in obstructive hydrocephalus series that includes aqueductal stenosis and

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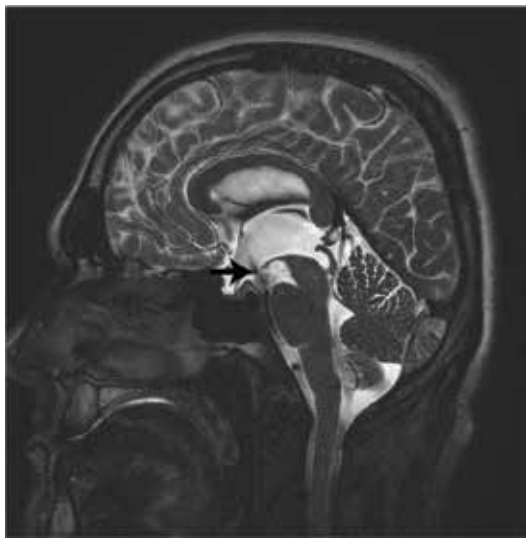

Figure 6. Flow void in T2-weighted sagittal MRI is clearly visible in the floor of the third ventricle after an ETV (black arrow).

tumors [23, 52]. However, communicating hydrocephalus cases have a rate of success about 50%. In patients who undergone shunt operations, ETV is still effective eliminating shunt dependency [59, 60]. Infants have worse outcomes in case of ETV according to literature. Failure rates vary between 20 and 50% [61]. Many authors recommend performing ETV in patients 2 years and older with their low success rates in infants [62, 63]. However, some authors indicate that ETV is still worth trying in these patients since the success rate is still considerable and a successful ETV provides long-term shunt independence [64, 65].

Radiographic features might be misleading as ventricular volume after EVD may not show an obvious change in the early preoperative period [66]. Early postoperative improvement and ventricular volume reduction are predictive values for the success of ETV as well as demonstrating flow void in the base of the third ventricle [67]. The patency of the ETV can be shown with flow void in T2-weighted images (**Figure 6**) and also with CSF flow cine MRI. Minor flow in the base of the third ventricle appears to be a bad prognostic factor for the patency of stoma [68].

Failure of ETV is in general due to the closure of fenestration in the third ventricle floor. The causes of the fenestration failure include the insufficient size of initial fenestration, reduced CSF reabsorption, arachnoid membranes in the prepontine cistern, hemorrhage obstructing fenestration, and late gliosis and postoperative infection. Failure rates can be as high as 50% in noncommunicating hydrocephalus series even with patent ventriculostomies [58].

6. Complications

The overall complication rate of ETV series is found to be 8.5% by Bouras and Sgouros [69]. The complication rates varied between 0 and 31.2%. Overall permanent morbidity rate was

2.38%, and the mortality rate was found 0.28%. Complications can be categorized as intraoperative, early postoperative, and late postoperative.

Neurovascular injury and bradycardia are the most common intraoperative complications. Various authors reported arterial and venous bleeding during the procedure [59, 63, 70]. Considerable intraoperative bleeding is reported almost 3.7% of the procedures, and about 4.2% of the ETVs is abandoned due to hemorrhage. Many authors reported different rates of intraoperative bleeding. But severe bleeding rates are low as 0.6%, and the rate of the most frightening intraoperative complication of ETV—basilar artery rupture—is as low as 0.2%. Pseudoaneurysm formation in the basilar tip after basilar injury is reported. Bradycardia is reported up to 41% during ETV [71]. A proposed mechanism for bradycardia is the generation of Cushing reflex due to irrigation and stimulation of hypothalamic nuclei. Even cardiac arrest is reported during an ETV performed for posthemorrhagic hydrocephalus [72].

Immediate preoperative complications include postoperative hemorrhagic complications like subdural hematoma, intraventricular hemorrhage, intracerebral hematoma, and epidural hematoma. The total rate of hemorrhagic complications is about 0.81%, and subdural hematoma being the most common hemorrhage [69]. A large corticotomy and sudden drainage of CSF are possible risk factors for development of subdural hematoma. Increased ICP of the subdural space also seems to be the cause of subdural hygromas. Central nervous system infections are one of the severe early postoperative complications. Meningitis or ventriculitis is recorded in 1.81% of the patients. Cerebrospinal fluid leak due to increased subdural pressure from corticotomy is also a postoperative concern as it can lead to CNS infections. Electrolyte and hormonal imbalances are reported in the literature. Systemic complications including syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus, and secondary amenorrhea are also found to be complications.

The most important late complication is the failure of the ETV. Sudden deterioration and death are reported in the literature, but it occurs rarely [73, 74]. As the risk of epilepsy being very low for this procedure, seizures are still a possible complication developing after ETV. Neurological morbidity is a possibility although rare with a total rate of 1.44%. Memory deficits may occur after ETV, and suggested hypothesis is fornix injury during the procedure. Fornix contusion is reported in ETV patients up to 16.4% [33]. Memory problems can be transient as well as permanent. Other than neuropsychiatric problems, hemiparesis, decreased consciousness, and gaze palsy are some of the rare neurological complications [69].

7. Conclusion

Endoscopic third ventriculostomy is a novel treatment for noncommunicating hydrocephalus. Safety and efficiency of the procedure are proven. Indications of ETV are expanding day by day with good results reported for various diseases. Compared to CSF diversion techniques, ETV is preferable for select cases with avoidance of shunt dependency and thus shunt complications.

Acknowledgements

We wish to acknowledge Dr. Altay Sencer of the Department of Neurosurgery, Istanbul University, Istanbul Faculty of Medicine, Istanbul, for his assistance.

Conflict of interest

Authors declare that they have no conflict of interest.

Thanks

We wish to thank Cristina Brinza for her illustrations.

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Chapter 8

Presentation of the Success Rate of ETV in Distinct Indication Cases of Hydrocephalus

Joachim M.K. Oertel and Akos Csokonay

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72889

Abstract

Endoscopic third ventriculostomy (ETV) is an endoscopic fenestration between the floor of the third ventricle and subarachnoid space. It is the procedure of choice for obstructive hydrocephalus (HC). The indication includes obstructive HC caused by aqueduct stenosis, tumors, brain infarction, cystic lesions, hematoma, postinfectious and posthemorrhagic HC, malformation of the fourth ventricle, and further uncommon indications. In this chapter, surgical techniques and the success rate of ETV in distinct indications will be presented and discussed. The overall success rate of ETV is reported at 60–90%. The outcome of the procedure depends highly on the underlying pathology and age. A very favorable outcome is reported in case of aqueduct stenosis (67–93.5%). High success rate is observed in case of cerebellar infarction (86%), tumors (56–81%), and intraventricular cysts (56–95%). In case of intraventricular hemorrhage (43–73%), infection (60–64%), anatomical aberration (21–80%), and communicating HC (65–72%), a significantly inferior success rate is reported. It is well known that ETV has a lower success rate in children (68–71%) compared to adults (70–90%). The overall high clinical success rate in short-term and long-term follow-up confirms that ETV is the gold standard for treatment of occlusive HC. It is effective, safe, and simple.

Keywords: third ventriculostomy, hydrocephalus, neuroendoscopy, success rate, indication

1. Introduction

1.1. Classification of hydrocephalus

Walter Dandy classified hydrocephalus as "communicating" or "noncommunicating" type based on examinations with ventricle and lumbar puncture in 1913. He considered hydrocephalus as "noncommunicating" or "obstructive" if after the injection of a colored solution in the lateral

ventricle, the dye did not appear in the spinal fluid removed by lumbar puncture. In contrast, if this solution appeared, hydrocephalus was classified as "communicating" [1]. This classification was simple and useful to understand hydrocephalus, but first was found inadequate to understand the pathophysiology [2]. The proposed classification is hydrocephalus without obstruction (true communicating hydrocephalus) in case of choroid plexus papilloma and with obstruction at the level of venous outflow (skull base anomalies and congenital heart disease), arachnoid granulations (hemorrhage and infection), basal cisterns (hemorrhage and infection), outlets of fourth ventricle (infection and Chiari malformation), Sylvian aqueduct (congenital anomalies and tumor compression), and foramen of Monro (congenital anomalies, tumor, and postshunt ventricular asymmetry) [2]. Nonetheless, the classic nomenclature remained in clinical practice due to its simplicity.

1.2. History of neuroendoscopy

The first neuroendoscopic procedure was introduced in 1910, when L'Espinasse performed a cauterization of plexus choroideus with a cystoscope. The other pioneer in neuroendoscopy was Walter Dandy. He published his results in 1913. Clarifying the physiology, Dandy performed plexectomy to cease the cerebrospinal fluid (CSF) production as a treatment for communicating hydrocephalus. In case of obstruction, he created an internal bypass for communication between the third ventricle and cortical subarachnoid space [2, 3].

The first endoscopic third ventriculostomy (ETV) was performed by William Mixter in 1923. This successful technique later served as a model for modern neuroendoscopy. He performed a perforation of the third ventricle floor by an intraventricular approach through the foramen of Monro. The invention of Hopkins optics, cold light sources, and digital cameras was a great development in the history of endoscopy. Following technical development and clinical application, neuroendoscopy spread over the world [3].

1.3. Endoscopic third ventriculostomy nowadays

For obstructive hydrocephalus, endoscopic third ventriculostomy is the procedure of choice. This is an endoscopic fenestration between the floor of third ventricle and subarachnoid space. The CSF flow can be restored and balanced out [4]. This procedure is considered effective, safe, and simple. The complication rate is lower as it has a lower infection rate; there is no foreign material and no overdrainage compared with shunt [4].

Nowadays, the use and role of endoscopic ventriculostomy expand continuously. It remains challenging to estimate and define the success of the procedure [5], even though many studies have overall focused on this topic [5–14].

2. Indications

In general, endoscopic third ventriculostomy is the gold-standard treatment for noncommunicating hydrocephalus. The indication for ETV includes all cases with obstruction between

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the third ventricle and the subarachnoid space with preserved CSF absorption from subarachnoid space into the venous system [2, 14, 15]. In case of obstruction at the level of Pacchionian granulation and venous outflow, performing ETV is definitely not recommended [14].

2.1. Aqueduct stenosis

One of most common etiology of obstructive hydrocephalus is the aqueduct stenosis [16, 17] (**Figures 1** and **2**). The obstruction can be congenital or acquired. In 75% of cases, it is idiopathic. In remaining cases, it can be caused by infections, hemorrhages, or malformation of the central nervous system or can be related to genetic factors [16]. The first and best treatment option for this is ETV. Ventriculostomy has a good outcome regardless of etiology of the stenosis, whether it is congenital, acquired, or tumor-related obstruction [14]. However, the success rate is different in certain cases of the aqueduct stenosis. It depends on the etiology, age, clinical, and radiological characteristics [13]. In certain cases, as an alternative treatment or even simultaneous, aqueductoplasty may be performed [7, 18]. The result of aqueductoplasty is comparable with the success of ETV. As alternative treatment, it may be useful in case of thick and tough floor of the third ventricle preventing the hypothalamus or vessel injuries [18].

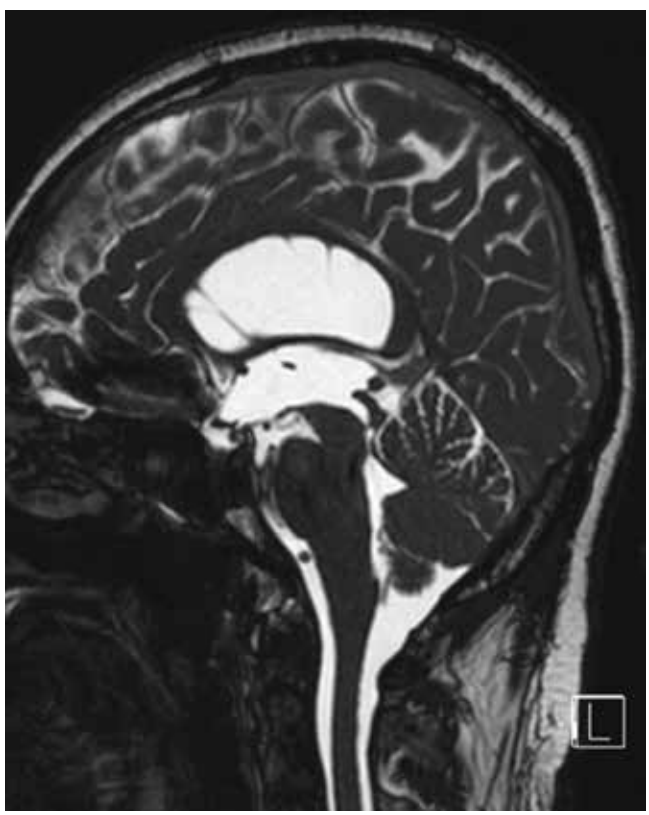

Figure 1. Aqueduct stenosis (MRI scan TRUFI sequence).

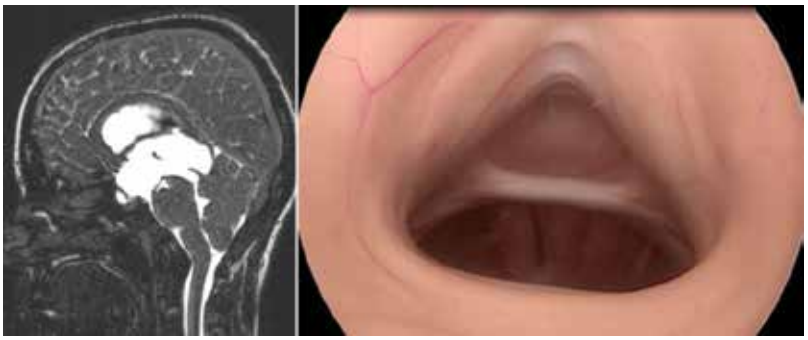

Figure 2. Aqueduct stenosis (left) MRI scan TRUFI sequence (right) endoscopic view.

2.2. Far distal obstruction

Obstruction distal to the fourth ventricle is a rare cause of hydrocephalus [19]. It can develop through intraventricular membranous obstruction [20, 21] or extraventricular compression [22] and in case of Dandy Walker syndrome [26] and Chiari malformation [23–25] (see below) [19]. Like all obstructive hydrocephalus, it may also be treated successfully with ventriculostomy, although an additional surgical technique with flexible endoscope is required (see below).

2.3. Tumors and cystic lesions

Endoscopic third ventriculostomy might be a surgical option in case of tumor- or cyst-related hydrocephalus, where the CSF flow disturbance is distal from the place of ventriculostomy (**Figures 3–5**). Therefore, in selected cases, it might be performed in case of tumor localization in the brainstem, posterior fossa, thalamus, pineal region, third and fourth ventricle, and other localization, e.g., cerebellopontine angle, frontal lobe, or diffuse growth pattern [27].

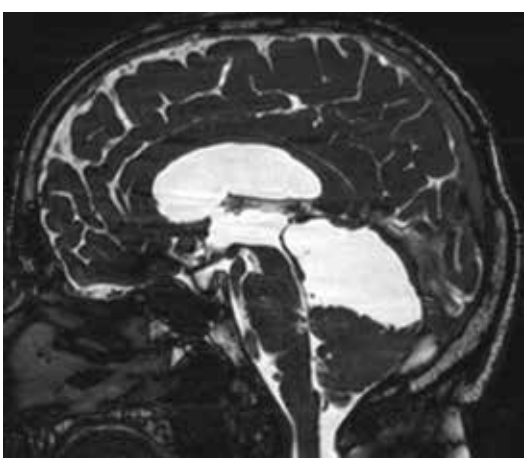

Figure 3. Arachnoid cyst with compression of the CSF pathway (MRI scan TRUFI sequence). In this case, a cystostomy and simultaneous ETV were performed.

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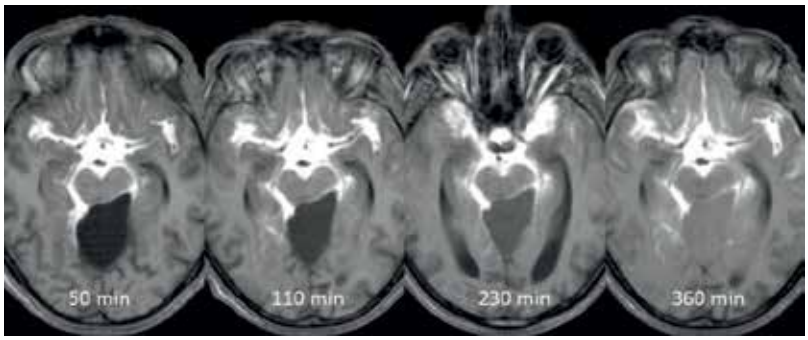

Figure 4. Arachnoid cyst with compression of the CSF pathway (cisternography). Same patient as in **Figure 3**.

In children, the posterior fossa is a common localization for various tumors (54–60% of brain tumors during childhood), and a hydrocephalus develops with high probability in these cases [13]. Frequent localizations are at the cerebellum, midline, brainstem, or cerebellopontine angle. Histologically the following tumors may occur: medulloblastoma, ependymoma, astrocytoma, ganglioglioma, cavernoma, primitive neuroectodermal tumor (PNET), meningioma, and others [28]. Gliomas in the midbrain and in the periaqueductal area are relatively rare and low grade. They show benign growth patterns, and malignant spreading is rare, although a suggested dissemination through CSF has already been reported [29]. The compression of the

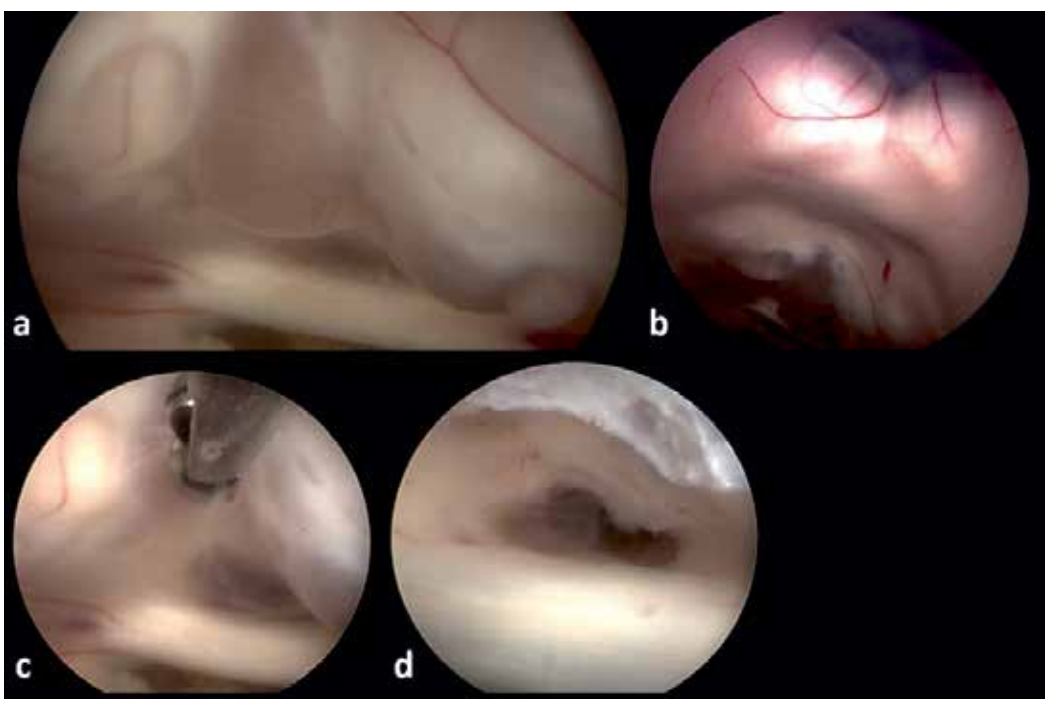

Figure 5. (a and b) Multiple cysts of the third ventricle with obstruction of the Sylvian aqueduct. ETV (see **Figure 9**) and cyst removal (c) were performed. (d) Free aqueduct.

fourth ventricle or the foramina of Magendie and Luschka leads to circulation disturbances and hydrocephalus [13]. ETV is recommended primarily for the treatment of children with midline posterior fossa tumor–related obstructions [30]. ETV can be combined with tumor biopsy, thus providing useful information for the diagnosis. In certain cases, even the tumor resection (e.g., third ventricle) might be performed [13, 30]. The resection alone can set the CSF pathway free, providing a normal CSF circulation. Therefore, performing ventriculostomy routinely is not recommended. After tumor removal, not only the causal problem of hydrocephalus might be solved. With performing the ETV an intraperitoneal spreading of the chemotherapeutic drugs through the shunt can be avoided [32]. The time of ETV in relation to the tumor resection is still under discussion [13].

Beside posterior fossa tumors, the indication expands to pineal tumors and third ventricle tumors [33]. The pathology of these is various. The pathology includes, but is not limited to glial tumors, ependymoma, pinealoblastoma, pinealocytoma, meningioma, germ cell tumors, primitive neuroectodermal tumor, teratoma, epidermoid, metastasis, and cysts [34, 35]. Colloid cysts, arachnoid cysts with extension in the ventricles or midline, and quadrigeminal cysts can be treated with endoscopic cystectomy, cystocisternostomy, cystoventriculostomy, ventriculocystostomy, and ventriculocystocysternostomy [36]. Even a combination with ventriculostomy may be performed [13].

2.4. Cerebellar infarction

Cerebellar infarction with space-occupying effect might lead to obstruction of the CSF pathway (**Figure 6**). The occurrence of stroke-related occlusive hydrocephalus is 10.9–27.2% of cerebellar stroke patients [37]. Deterioration of consciousness in case of cerebellar infarction can be caused by compression of the brainstem through increasing parenchymal edema or by hydrocephalus. A neurosurgical intervention is required in case of decline of consciousness [7, 37, 38]. For treatment of hydrocephalus, the alternative options are external ventricle drainage (EVD), shunt placement, and ETV. However, not every hydrocephalus caused by cerebellar infarction is a suitable candidate for ETV. In case of patients with severe deterioration of consciousness and/or brain stem compression, an adequate decompression should be performed [37]. In case of hydrocephalus, the high risk for infection in case of long-term ventricle drainage can be avoided with third ventriculostomy. The compression of prepontine cistern usually does not cause any surgical problems; the technique can be performed in the usual way [37]. Regarding the routine intracerebral pressure (ICP) monitoring in case of ETV patients, it is not recommended, as the level of the consciousness is an indicator for the success of ETV, and postoperative CT scan is performed to also control the ventricle size. There are many positive experiences concerning ETV procedures without routine ICP monitoring [12, 37].

2.5. Hemorrhage-related obstructive hydrocephalus

An obstruction of CSF pathway can occur in case of intraventricular or intraparenchymal bleeding with or without intraventricular extension, cerebellar hematoma, or subarachnoid hemorrhage [39, 40]. In case of intraventricular or intraparenchymal bleeding related to obstructive hydrocephalus, ETV can be an alternative to EVD placement (**Figure 7**). However,

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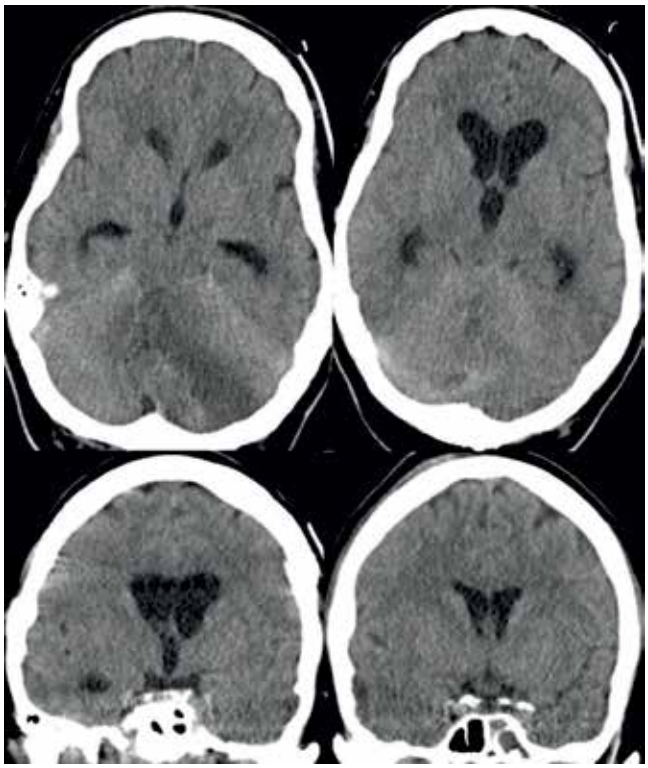

Figure 6. Obstructive hydrocephalus in case of cerebellar infarct (left above and below) preoperative CT scan—dilatation of temporal horn and frontal horn of lateral ventricle and third ventricle (right above and below) postoperative CT scan, reduced size of ventricle system.

only a small percentage of patients with the above-mentioned pathology are optimal candidates for ETV and its indication is rare [7, 39]. The gold standard for treatment of hemorrhage-related acute hydrocephalus remains EVD placement. Acute hydrocephalus can arise either by intraventricular hemorrhage or by intraparenchymal hematoma with space-occupying effect compressing the CSF pathway. There are advantages and disadvantages of preforming an ETV. The endoscopic procedure might reduce the risk of the drainage-related infections and reduce the numbers of surgical procedures, as the drainage has to be changed after 7–10 days. In most cases, it is required to remove the blood clot. With endoscopic procedure, the possibility is provided; however, this procedure can be time-consuming. In case of intraventricular bleeding, the endoscopic view is unclear. The visualization can be normalized through forced irrigation, but in case of a severe hemorrhage, the visual quality remains poor despite prolonged irrigation. The space-occupying intraparenchymal hemorrhage can displace the ventricles depending on the localization. Furthermore, the anatomy of the prepontine space and basilar artery might be distorted increasing the risk of basilar injury. In the acute phase, the floor of the third ventricle is thick in contrast to the subacute and chronic obstruction. This fact likewise causes a higher risk for basilar injury. These findings lead to technical challenges in the endoscopic procedure [39].

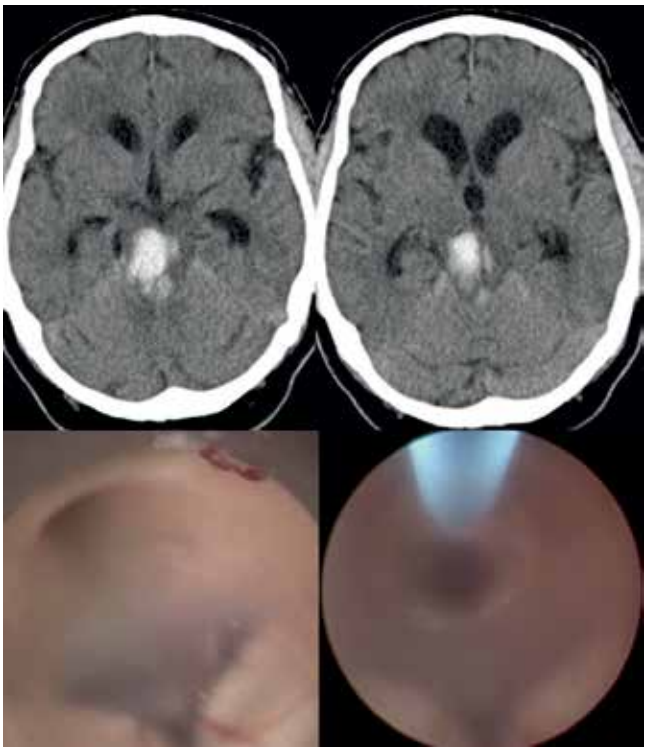

Figure 7. Intraventricular hemorrhage of forth ventricle with occlusive hydrocephalus. Obscured view due to the bleeding (above) and preoperative CT scan (left below) landmarks of third ventricle—infundibular recess, mammillary bodies (right below), balloon dilatation.

The clinical results are primarily influenced by the parenchymal damage. It is recommended to perform an ETV if the requirement of continuous ICP monitoring and liquor drainage for ICP reduction is excluded. In certain cases, where the CSF obstruction plays the dominant role and the hemorrhage does not have significant space-occupying effect, ETV might be the optimal option [39]. In these cases, the clinical condition can be dramatically improved. In all other cases, ETV should be considered if weaning the patients off the drainage is not successful within a week. As mentioned above, the standard treatment remains EVD placement. Thus, in case of doubt, EVD placement should be performed, even leading to an interruption of ventriculostomy [39].

2.6. Infection-related hydrocephalus

Despite the indication in postinfectious hydrocephalus (meningitis, ventriculitis, and shunt infection) with impaired CSF absorption, or ductal, foraminal obstruction is controversial, ETV might be also successful in certain cases. As consequence of the infection, cisternal scarring might occur, leading to higher failure rate [40]. Regarding the etiology in children, the occurring pathogen depends on the age. Hydrocephalus following prenatal infections may be caused by Toxoplasmosis or Cytomegalovirus. In neonatal period, the most frequently occurring bacteria

are Gram-negative bacteria during the first 14 days of age and Gram-positive bacteria after the first 2 weeks of age. Further pathogens may be Candida species at this age of life. In postnatal period, hydrocephalus may be caused by bacterial (such as Haemophilus influenzae type B), viral, or fungal (such as Cryptococcus) infections [41]. In adults, the infection can be bacterial (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Listeria monocytogenes*, and group B Streptococcus), viral (most frequently Enteroviruses), or fungal (Cryptococcus species) [42].

The tuberculous meningitis–related hydrocephalus is discussed separately, because of peculiar pathological behavior. It is still a frequent disease in the developing countries [43]. As hematogenous dissemination from primary complex, tuberculous foci might be deposited in the cortex, meninges, choroidal plexus, or ventricular wall, and through rupture into the subarachnoid space, it leads to meningitis [44]. In acute phase, there is an acute inflammation in ventricles with ependymal infection and tuberculous exudate. Although the exudate can be washed out during ETV, ventriculostomy is more difficult due to acute inflammation and anatomical changes [14, 45]. In the chronic phase, the aqueduct can be obstructed by exudates, small tuberculomas, or infection of ependyma. In this phase, the procedure has a higher success compared to the acute phase; however, the floor of the third ventricle is thickened, which could complicate the surgery [40].

2.7. Congenital malformation–related hydrocephalus

Central nervous system (CNS) anomalies might lead to congenital hydrocephalus. The most common cause is the congenital aqueduct stenosis as mentioned above. It can be caused by infection, hemorrhage before birth, or tumors [16]. In this case, endoscopic ventriculostomy is the treatment of choice. Ventriculostomy might be also a surgical alternative in case of Chiari I and II malformation with fourth ventricle outlet obstruction, myelomeningocele, syringomyelia, and Dandy-Walker malformation–associated hydrocephalus [13, 19, 26, 46, 47]. The success of ETV in these cases is diverse.

Hydrocephalus develops in considerable number in cases with neural tube defect [47, 48]. The incidence of hydrocephalus in patients with meningomyelocele increases after closure the defect [48]. Performing the endoscopic procedure may be technically difficult, due to the anatomical variations (enlarged interthalamic adhesion, stenosis, or atresia of foramen of Monro and so on) [47]. Chiari malformation can be concurred either with communicating or with noncommunicating hydrocephalus. Although ETV may be a good alternative for shunt placement in these cases, the success depends highly on the optimal selection of cases for endoscopic procedure [25]. In case of obstructive hydrocephalus, there is a better chance for success. The majority of Dandy-Walker syndrome (DWS) is associated with hydrocephalus [26]. In this case, the primary treatment continues to be controversial. In general, the initial treatment remains the shunt placement. Endoscopic excision of obstructing membrane as initial procedure is not recommended because of the associated risks for morbidity and mortality. ETV may be an alternative for shunt placement in patients with frequent shunt malfunction. In DWS concurred with aqueduct stenosis, the combination of ventricle-cyst stenting and ETV may be performed [26].

2.8. Obstruction due to giant aneurysm

An obstructive hydrocephalus through giant aneurysm is rare, but it has been already reported in some cases [49–52]. Commonly, these cases are treated via shunt placement, although an aneurysm growing after shunt implantation has been already reported. The theory is that the decreased intracranial pressure after shunt placement reduces the tamponade effect, leading to aneurysm expansion and an increase in the risk for rupture [51].

In certain cases, an endoscopic ventriculostomy might be performed [49, 50]. Even though the anatomy is commonly changed as a consequence of the aneurysm (e.g., the third ventricle or aqueduct may be compressed and the anatomical structures as the floor of ventricle and mammillary bodies may be displaced), the landmarks can be identified and the surgery can be performed in the usual way [49].

2.9. Further indications for ETV

Every surgical revision after shunt implantation is considered as shunt failure. Many studies established that endoscopic third ventriculostomy in shunt failures might be an effective treatment option (**Figure 8**). The presence of shunt failure does not exercise influence on the failure rate of ETV. However, the success seems to be diverse in certain etiology groups [14].

It was observed that hydrocephalus patients less than 65 years of age with idiopathic normal pressure, where the dominant symptom was gait disturbances and only minimal cognitive deficits could be observed, had a good success rate [14].

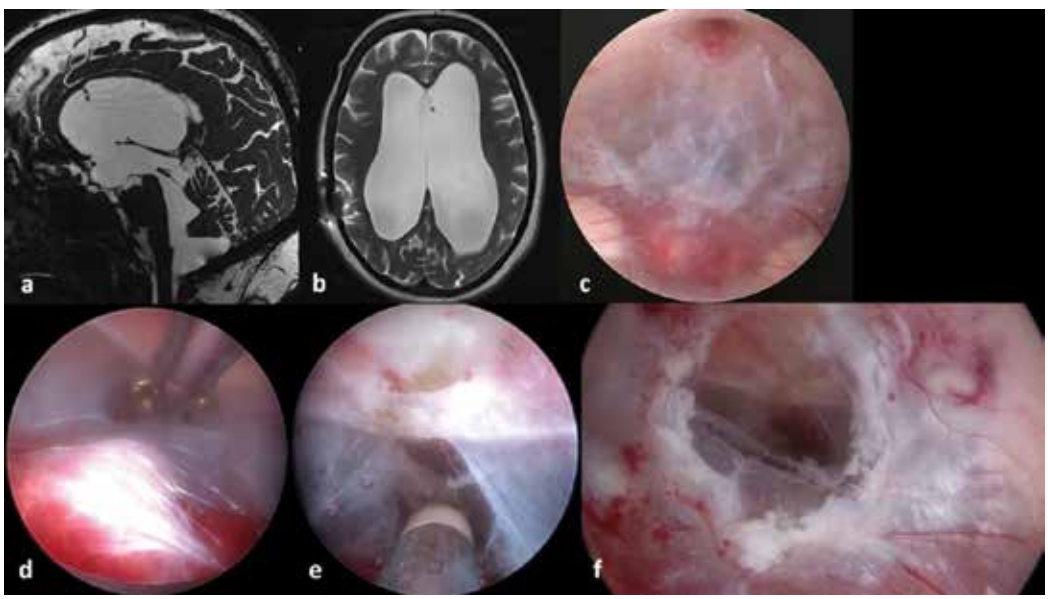

Figure 8. Hydrocephalus with shunt malfunction (a and b) preoperative MRI scan, (c) scarred thick floor of the third ventricle, (d) perforation of adhesions in the prepontine cistern with forceps, (e) with bipolar diathermy, and (f) view on the cisterns through the ventriculostoma.

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3. Surgical technique

3.1. Neuroendoscopic equipment

For endoscopic ventricular surgery, either rigid or flexible endoscope can be used. Rigid endoscopes have a higher image quality and allow an easier insertion and handling of instruments. In contrast, the flexible one allows a flexible mobility of the scope, even though producing a lower image quality [53]. Endoscopic equipment for ETV includes various rigid rod lens Hopkins optics and instruments (scissors, hooks, puncture needles, forceps for tumor biopsy and grasping, bright cold Xenon light source, HD video camera system, irrigation device, and Fogarty balloon catheter) [7].

3.2. Surgical technique

The operation is performed under general anesthesia. The patient is placed in supine position, the head in 3-pin fixation and tilted slightly forward. The hair is shaved and the approach is marked. The standard placement of the burr hole is anterior to the coronal suture and 2 cm lateral to the midline. After skin disinfection and sterile draping of the operating field, the scalp is incised in a straight line, about 2–3 cm long. After placement of the burr hole (about 1 cm) and opening the dura, the operating sheath is introduced into the lateral ventricle and the trocar is inserted at about 5 cm depth of dura. The endoscope is fixed and the trocar is removed. The rigid 0° diagnostic optic is inserted for inspection and identification of the main landmarks. In the lateral ventricle, the fornix, the foramen of Monro, and the choroid plexus are identified (**Figures 9** and **10**). Under direct visual control, the endoscope is advanced through the foramen of Monro into the third ventricle. In the third ventricle, the main landmarks are the mammillary bodies and the infundibular recess. The diagnostic inspection is extended with

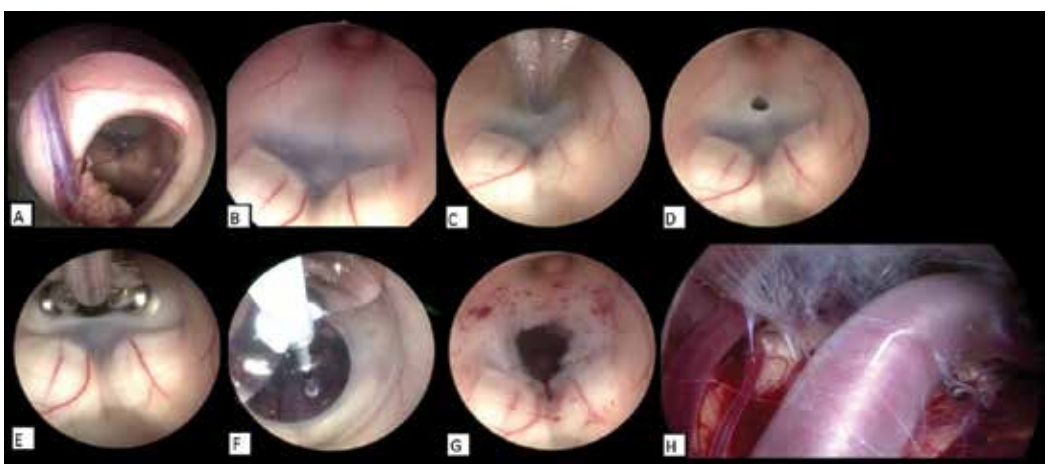

Figure 9. Steps of endoscopic third ventriculostomy. (A) View of foramen of Monro, plexus choroideus, anterior septal vein in lateral ventricle, (B) view of mammillary bodies, infundibular recess in the third ventricle, (C) ventriculostomy with bipolar diathermy, (D) ventriculostoma, (E) enlarging with perforation forceps, (F) dilatation with Fogarty balloon catheter, (G) expanded ventriculostoma, and (H) view of basilar artery.

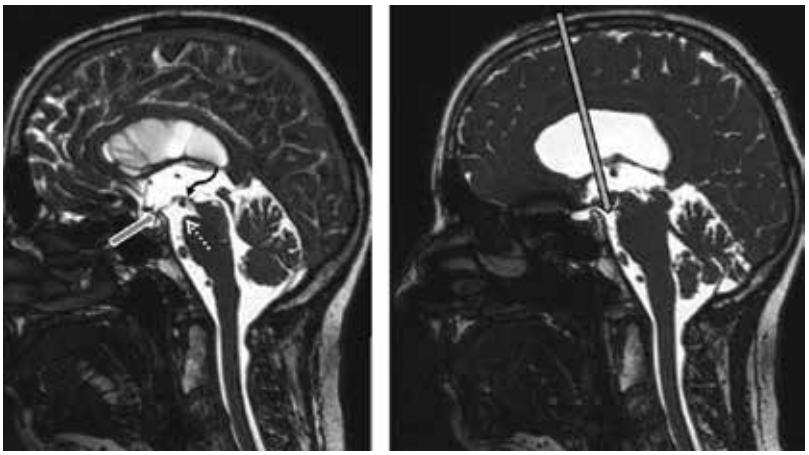

Figure 10. (Left) Landmarks on the MRI scan TRUFI sequence, (L) lateral ventricle, (III.) third ventricle. Infundibular recess (grey arrow), mammillary body (wavy arrow), and interpeduncular and prepontine cistern (dotted arrow). (Right) Entry point.

30°, 45°, and/or 70° optics to view the anterior and posterior parts of the ventricles if applicable. It can be useful in case of obstruction of the aqueduct or tumor. In the midline between the mammillary bodies and the infundibular recess, the perforation is performed. For fenestration, there are several possibilities. The perforation can be performed by sharp perforation with semisharp probe [54], by blunt perforation with the endoscope itself, the balloon catheter itself [8], by coagulation with monopolar or bipolar diathermy [7, 8, 54], and by laser perforation [54, 55], waterjet dissection [55], ventriculostomy forceps [7], or ultrasonic probe [56]. It is recommended to use a blunt perforation to avoid vascular injury [8, 55]. In case of thick ventricle floor, it is recommended to use cauterization with bipolar diathermy at low energy [7, 8], sharp perforation with semisharp catheter [54], or waterjet dissection [55]. However, laser perforation and monopolar diathermy should be avoided [8]. After the perforation by a rigid instrument, enlarging ventriculostomy is initially performed by a perforation forceps and subsequently by inflation of a Fogarty balloon catheter (4–7 mm). After ventriculostomy, an inspection is performed with the 0° diagnostic optic to identify the dorsum sellae and the tip of the basilar artery to ensure free CSF flow. If a Liliequist membrane or subarachnoid adhesions are present, they also should be perforated (**Figure 8**). While withdrawing the operating sheath, an active bleeding at the foramen of Monro or at the corticotomy should be ruled out. After removal of instruments, a gelatin sponge is inserted in the burr hole and the galea is tightly closed to avoid a subgaleal CSF accumulation and leakage. The skin is sutured with clamp or thread. As standard, no EVD is inserted (**Figure 1**) [7, 9].

In case of infants up to 2 years of age, the procedure is performed in the same way; the only exception is that the head is fixed with bandages running over the forehead [57].

In addition, a flexible endoscope can be used for transaqueductal inspection. Following ETV, the work sheath should be moved posteriorly to achieve a straight approach to the Sylvian aqueduct. If the size of diameter of the aqueduct allows it, the working optic can be withdrawn and

the fiberscope inserted. After forwarding the fiberscope through the aqueduct, the patency of outlets of the fourth ventricle can be inspected. The fiberscope is withdrawn and a 0° diagnostic optic inserted to check for contusion or bleeding during the withdrawal of the work sheath [19].

4. Success rate of distinct indications

In case of a successful third ventriculostomy, the symptoms mostly improve soon after surgery. Most of the patients, who suffered from deterioration of consciousness because of obstructive hydrocephalus, show a rapid improvement after the surgery [6]. Of course, it requires an adequate indication and it depends considerably on the underlying pathology [6, 7, 12] (**Table 1**).

Postoperative CT scan is routinely performed; however, the radiological findings alone do not count as an indicator of ETV success. It must be assessed in all cases with the clinical findings [6, 10, 58, 59]. After ETV, the intraventricular pressure does not decrease immediately in certain cases [10]. The ventricle size can increase, decrease, and remain unchanged after ventriculostomy [6]. In most cases, the ventricle size might correlate with the clinical outcome as early as 1 month after the surgery. In successful cases, a significant decrease can be seen, while it is not observable or not significant in ETV failures [58, 60]. Especially, decreasing of the third ventricle size is

Indication	Success rate (%)	References
Aqueduct stenosis	67–93.5	Vulcu et al. [6], Grunert et al. [9], Hellwig et al. [10], Hopf et al. [11], Moorthy et al. [14], Oertel et al. [63], Gangemi et al. [65]
Far distal obstruction	72–76	Oertel et al. [31], Mohanty et al. [26], Warf et al. [47]
Tumors	56–81	Vulcu et al. [6], Oertel et al. [7], Grunert et al. [9], Hellwig et al. [10], Hopf et al. [11]
Cysts	56–95	Vulcu et al. [6], Oertel et al. [7], Hopf et al. [11], Moorthy et al. [14], Ray et al. [27], MacArthur et al. [69]
Cerebellar infarction	86	Oertel et al. [7], Baldauf et al. [37]
Hemorrhage	43–73	Vulcu et al. [6], Oertel et al. [39], Grunert et al. [9], Siomin et al. [40], Roux et al. [73]
Infection	60–64	Mugamba et al. [13], Siomin et al. [40], Oertel et al. [63]
Tuberculous meningitis	60–83	Singh et al. [74], Bhagwati et al. [43]
Congenital malformations	21–80	Wu et al. [25], Mohanty et al. [26], Rei et al. [46], Warf et al. [47]
Giant aneurysm	No adequate data	
Further (e.g., noncommunicating HC)	65–72	Hellwig et al. [10], Moorthy et al. [14], Gangemi et al. [75]

Table 1. Success rate of ETV in distinct indication cases.

reliable [60]. The ventricle size decreases to smaller size as measured preoperatively but remains still bigger than in healthy patients. It shows presumably that the absorptive mechanisms do not work as well as in healthy patients and the successful ventriculostomy provides a compensated communicating hydrocephalus [61]. The postoperative examination can be supplemented by MRI scan. The presence of CSF flow void, which refers to signal loss in the MRI occurring with CSF, may indicate the success [58]. It is important to emphasize that even without any changes in the ventricle size, the patient can improve clinically as a result of successful ventriculostomy.

The overall success rate of ETV is reported at 60–90% [6–12, 62] (**Table 2**). The initial success rate in the early postoperative evaluation is higher than during long-term follow-ups [6, 63]. Different data regarding the success rate can be explained by the different definitions of ETV success and with the fact that lots of studies examined mixed population regarding the age, the underlying pathology, the time course of the follow-up, and the strategy of patient selection [6–8]. Based on the experience and on the data, it is recommended to define the clinical success of third ventriculostomy as needless of re-ETV or shunt placement 3 months after the surgery [6, 63]. However, there is no common agreement regarding the point of time when a ventriculostomy is considered completely functional. In contrast, according to a Canadian experience, the success strictly means "no further CSF diversion procedures" [64].

As many studies have established, the success rate of the procedure depends highly on the underlying pathology and the age of the patients [6, 7]. Furthermore, the outcome is influenced by the indications and the performing neurosurgeon [12]. An ETV Success Score (ETVSS) was developed by Kulkarni et al. to estimate a 6-month outcome taking age and etiology into account. The success score is recommended to be used while selecting the optimal candidate for ETV. Even though ETVSS was initially developed to predict the short-term success, the score likewise correlates with the long-term outcome. The score ranges between 0 and 90, where 0 means extremely poor chance for success and 90 means very good chance for success. Regarding the success rate, the patients might be divided into three groups: high ETVSS-Group ≥80, moderate ETVSS-Group 50–70, and Low ETVSS-Group ≤40. The optimal candidate for ETV seems to be the patient over 10 years of age with obstructive hydrocephalus as aqueduct stenosis or tectal tumor and without infection, cerebral hemorrhage, or previous shunting in case history [5].

4.1. Aqueduct stenosis

Endoscopic ventriculostomy has the most favorable outcome in case of benign aqueduct stenosis (67–93.5%) [6, 7, 9–11, 14, 63, 65]. This fact supports the assumption that the therapy of

Age group	Overall success rate (%)	References
Adults	60–90	Vulcu et al. [6], Schroeder et al. [8], Grunert et al. [9], Hellwig et al. [10], Hopf et al. [11], Sacko et al. [12], Siomin et al. [62]
Children > 2 years	66–71	Vulcu et al. [6], Grunert et al. [9], Baldauf et al. [80], Oertel et al. [81], Beems and Grothenius [82], Etus et al. [83]
Children < 2 years	22–67	

Table 2. Overall success rate considering the age groups.

choice is ETV. Nevertheless, the success rate in each case depends on the etiology, age, clinical findings, and radiological characteristics [13]. The presence of aqueduct obstruction with free prepontine cistern is associated with significantly better outcome of ETV [66]. Regarding the etiology, the acquired stenosis has a better success result than the congenital form [67]. The clinical manifestation of the congenital form appears earlier than the acquired one, which contributes to the lower success rate. In infants, the success of the procedure seems to depend on the age as well as on the etiology. Under the age of 1 year, ETV also has higher success rate in case of aqueduct stenosis than in case of other etiology, although significantly less than in older children [9, 68]. Regarding age, the success seems to be related not only to the age at the time of the surgery but also to the age at onset of the pathological changes [13]. The different range of success rate derives from the fact that the studies examine mixed population regarding age and pathology [16] .

4.2. Far distal obstruction

Obstruction distal to the fourth ventricle is a rare cause of HC, but in any case, ETV might be a successful treatment with 72–76% of postoperative success [19, 26, 47].

4.3. Tumor and cystic lesions

The intraventricular, pineal region, infratentorial tumor- and cyst-related obstructive hydrocephalus has a high success rate after third ventriculostomy (56–81%, in cysts over 90%) [6, 7, 9–11, 63]. The best candidates seem to be patients with aqueduct obstruction in case of tectal tumors, pineal region tumors or cysts, and third ventricle tumors [11, 15, 27]. Simultaneously performing tumor mass resection or biopsy is also possible in certain cases. The success of ventriculostomy with simultaneous tumor removal or biopsy is reported [7, 69]. Another option is to perform ventriculostomy before or after the tumor surgery. There are diverging opinions on the timing [14]. The preceding ventriculostomy may reduce the chance for postoperative hydrocephalus in case of posterior fossa tumors [70, 71]. In case of cysts, a cyst resection or a fenestration between the cyst and the ventricle simultaneously may be performed to ETV. The success rate in these cases reaches 56–95% [6, 7, 11, 14, 27, 69]. After tumor removal, the cause of obstruction can be eliminated restoring the normal CSF flow. Therefore, performing ETV routinely is not necessary [32]. In case of posterior fossa tumors, higher success is established if hydrocephalus persists after tumor resection [72]. On the other hand, there are studies where the rate in case of tumors is significantly lower (56%) [6]. The different data can be explained by the fact that many studies do not differentiate between benign space-occupying lesions and progressive tumors; however, there is a significant difference between the two groups regarding the outcome [11]. The success of ETV depends on the localization and the growth pattern of the tumor. A progressive tumor is more likely to close the ventriculostoma earlier than a benign lesion or cysts. The same applies to a lesion in the third ventricle compared to an infratentorial tumor, which has no direct connection to the new CSF flow diversion. Likewise, the duration of the symptoms seems to be an influencing factor [7]. Regarding the surgical technique, it can be performed in a relatively uncomplicated way, but the obscuration of the ventricle anatomy by the tumor might cause difficulties [10, 14].

4.4. Cerebellar infarction

A cerebellar ischemic stroke might lead to obstruction of CSF pathway through the parenchymal edema. The occlusion can be treated with EVD or ETV depending on the endoscopic experiences of the surgeon. The ideal management is still controversial. An endoscopic ventriculostomy might be recommended if no brainstem compression exists [37]. The overall success of ETV in this case is about 86% [7]. Under certain circumstances, this etiology seems to be ideal for ETV, probably because of the acute onset and the pure obstructive origin [7]. The main indicator for successful ETV seems to be the level of consciousness. In case of no improvement of deteriorated consciousness despite ventriculostomy or in case of brainstem compression, a suboccipital decompression is required [37].

4.5. Hemorrhage-related obstructive hydrocephalus

The optimal management in case of hemorrhage-related obstructive hydrocephalus is still controversial. The overall success rate is 43–73% [6, 9, 39, 40, 63, 73], which is significantly lower than in other etiologies mentioned above. In this case, a difference was also established regarding the outcome in various age groups. The younger population has a lower success rate than the adult group. Moreover, in combination with infection, the rate is about 23% [40]. Evaluating the success of ETV remains difficult in any case, because of the adverse prognoses and clinical status in case of extensive intraparenchymal or intraventricular hemorrhage [39].

4.6. Infection-related hydrocephalus

The overall success rate amounts for about 60–64% in case of obstructive hydrocephalus caused by infection [13, 40, 63], even though adults benefit more from the procedure than children [13, 40]. The success of ventriculostomy depends on whether a prepontine scarring exits. In many case, ETV cannot be performed, because of intraventricular, ependymal scarring and anatomical distortion. In contrast, an obstruction, especially of the Sylvian aqueduct in postinfectious hydrocephalus, promises a better outcome [45]. As mentioned above, infection combined with hemorrhage has a lower success rate [40].

In tuberculous meningitis, the exudate is deposited in basal cisterns leading to an obstruction at the level of Sylvian aqueduct, at the outlet of fourth ventricle, or in the subarachnoid space [14]. ETV success amounts for about 60–83% in this case [43, 74]. The difference of the success depends highly on the thickness of the ventricle floor and the presence of the exudate. In acute phase, the tuberculous exudates in ventricle system and subarachnoid space and the inflammation of ependyma may impede the surgery and lead to lower success rate [14].

4.7. Congenital malformation–related hydrocephalus

Although opinions vary widely about the role of ventriculostomy in congenital CNS malformation–related hydrocephalus, it may be a successful option in certain cases [13, 26, 46, 47]. The overall success rate in case of brain malformation–related hydrocephalus amounts to 21–80% [25, 26, 46, 47]. These various rates may be explained by the fact that most surgeries are performed in infancy, which considerably influences the outcome. Moreover, obstructive hydrocephalus

overall has a higher ETV success rate compared with noncommunicating hydrocephalus. In patients with meningomyelocele, the success may be higher if ETV is combined with choroid plexus cauterization [47]. In case of Chiari malformation type I and syringomyelia-related hydrocephalus, a shunt independency with a high rate of causing a high ETV success may achieved [14]. The reduction of the caliber, even a resolution of the syrinx, was observed [13, 14].

4.8. Obstruction due to giant aneurysm

Successful endoscopic ventriculostomy was reported in some giant aneurysm–related obstruction [49, 50]. The most feared complications are related to vascular injury leading to infarction, hemorrhage, or pseudoaneurysm development [49]. Although, as mentioned above, some successful ETV was reported, where the procedure seemed to be a good option for treatment of obstructive hydrocephalus, the experiences and reports in these cases are wanting.

4.9. Success in cases of further indications for ETV

In case of normal- and low-pressure hydrocephalus and malabsorptive hydrocephalus, the success rate amounts about 65–72% [10, 14, 75]. In patients less than 65 years of age and with communicating hydrocephalus, with only minimal cognitive deficits, where the dominant symptom is gait disturbance, the success rate is comparable with the rate after shunt placement [14].

The success in case of shunt malfunction or infection was observed in similar percentage of 67–80% [14, 76]. An exact indication for ETV in communicating hydrocephalus and shunt malfunction has not been defined yet, but as it can be seen, it may be an alternative in certain cases.

As mentioned earlier, patients with shunt malfunction might be treated successfully with ETV in certain cases as well. It is clear that a patient with aqueduct stenosis benefits more from ventriculostomy following shunt malfunction than patients with other etiologies. Consequently, ventriculostomy can be recommended in case of shunt malfunction if an obstruction exits in the CSF pathway. In contrast, patients without obstruction should be treated with shunt revision [77]. Following ventriculostomy, it is recommended to remove the shunt system to avoid the intermittent CSF diversion through the shunt [14].

4.10. Children

The debate is still open, whether the etiology or the age is the determining factor of ETV success in children. The overall success rate reaches about 66–71% in children [6, 7, 9]. In children under 2 years of age, having the chance for a success is significantly lower (22–67%), and infants under 6 months have the worst chance for restoration of the CSF circulation [6, 7, 9, 78–81]. While trying to predict the success using ETVSS, the age plays an important role [5]. The outcome has been examined in several studies regarding the underlying pathology in children, and the difference was also conspicuous between the various etiology groups [9, 78, 80, 81]. The final results correlate with data in adults. Patients with aqueduct stenosis overall have very favorable outcome [9, 78, 81]. Despite all these data, there are studies where no difference regarding the age [4] or etiology [82] was found. Nevertheless, based on the experiences and studies, the outcome seems to depend both on the underlying pathology and on the age [78, 83, 84].

5. Failure rate and complications

5.1. Complications and their prevention

Endoscopic ventriculostomy is considered less noninvasive and safe. The complications are rare and mostly related to the surgical procedure [85]. The average morbidity is 8.5% and mortality <1% [8, 11, 31, 85]. Permanent deficits are rare with an average value up to 2.38% [85], while the transient morbidity ranged up to 7.8% [8, 85].

The most feared complication is the vessel injury. Minor hemorrhage can be caused by small vessel injuries, for example in the cortex, brain parenchyma, choroid plexus, or margin of ventriculostoma during inflation of the Fogarty catheter. Minor hemorrhage can be managed with irrigation to achieve a tamponade effect [8, 55, 85]. In case of insufficient irrigation, coagulation with bipolar diathermy should be performed [8]. Major hemorrhage caused by injury of basilar artery and basilar perforating vessels, thalamostriate vein, or anterior septal vein injury can lead to uncontrollable hemorrhage and life-tethering situation with fatal outcome. Minor hemorrhage occurs in up to 16.5%, whereas major ones occur only in 0.49% [85]. These may occur for example due to false placement of instruments [7]. Brain nerve injury may occur in the same way [7, 85]. In many diseases such as developmental anomalies and tumors, the anatomy is distorted making the surgical technique difficult [85]. By using a rigid endoscope and correct position of fenestration, these complications can be avoided. Thorough inspection of the anatomical relationships on the preoperative MRI scan is essential.

Further complications may be epidural or subdural hematoma [8, 86–88], fornix contusion [8, 31], traumatic damage of thalamus and hypothalamus with endocrine and electrolyte disturbances [31, 85], hemodynamic alterations [6, 85], cerebral herniation syndrome in case of obstructed outflow channel or excessive irrigation [8, 85], CSF leakage [8, 85], abandoned procedure, or ETV failure (see below) [6, 12, 62, 63, 89]. The incidence of abandoned procedure ranges from 0 to 26% [8]. The most frequent causes are hemorrhage, complex anatomical circumstances, or inability to fenestrate the ventricle floor [8]. Postoperative infection may lead to meningitis, ventriculitis, brain abscess, or sepsis. Further nonspecific complication as thrombophlebitis, pneumonia, or wound infection may occur.

Summarizing, to prevent the complications, individual anatomical variations should be evaluated in the preoperative imaging. The relationship between the third ventricle floor and basilar artery should be thoroughly considered. The adequate technique with rigid instrument should be used and one has to consider the correct energy intensity and sources. As mentioned above, it is recommended to use low energy (maximum 10 W) and to avoid laser and monopolar diathermy. The correct placement of fenestration is essential; ideally, it is placed halfway between the mammillary bodies and infundibular recess in the midline. However, individual variations should be considered. After the perforation, the interpeduncular and prepontine cistern should be inspected and adhesions or the Liliequist membrane should be perforated.

5.2. Failure rate and re-ETV

Re-occlusion of the ventriculostoma is rare. Kulkarni et al. have reported that ETV has an initial higher failure rate in contrast to shunt placement, although it gets lower over time [5]. Most failures (58–97%) occur within the first 3 months [6, 7, 12, 62]. Within the first year, ETV failure reaches 16–20% [6, 62]. However, it might also develop after years; therefore, a long-term follow-up after the surgical procedure is required [12, 62, 89]. It remains controversial, whether re-ETV or shunt placement is the optimal choice of treatment for ETV failure. The decision depends on the age, etiology of hydrocephalus, imaging finding, and the duration between ventriculostomy and failure [63, 90]. In certain cases, repetition of ventriculostomy as the first choice is recommended, as a similar long-term success of 51–89% is expected [7, 16, 62, 63, 89, 91–94]. Some authors differentiate early failure from late failure, but the distinction between the two definitions is various (7 days—6 months) [4, 63, 89, 91, 93]. Multifactorial etiology including malabsorptive component, complications including hemorrhage and infection or technical failure as inadequate size of stoma with insufficient CSF flow through the stoma, and unperforated Liliequist membrane could be responsible for early failure [4, 63, 89, 93, 94]. The ideal size of stoma is not defined, and it seems to depend highly on the anatomy, while in case of a size between 4 and 7 mm, failures were also reported [89]. To avoid an intermitting CSF diversion through the shunt, ligature or removal of the shunt system is recommended, as mentioned above. Late failure could be caused by secondary closure as tumor progression, gliosis, and developing of membranes and adhesions in the subarachnoid space [4, 6, 11, 89, 91]. In children, the absorption of CSF at the Pacchionian granulations is immature [95], which may play a role in ETV failure. Further cause for failure might be the multifactorial etiology in certain cases [4]. The success of re-ETV is found higher in case of late-repeat-ETV than in early ones [63, 91, 96], although there are some controversial results [62]. As indicated above, the failure rate decreases during the follow-up [63]. Regarding the age, the results are controversial, but in most studies, higher failure rates are reported when less than 6–24 months of age [4, 63, 89]. Regarding the pathology, the failure rate amounts 10–20% in aqueduct stenosis, while in other indication cases, it amounts up to 50% [14]. If no obstructive cause for failure is seen on the MRI scan, a shunt placement is considered [63] taking a multifactorial etiology including malabsorptive mechanism as cause of failure. Re-ETV is also not recommended in case of tumor progression–related closure [89]. There are no exact criteria defined for repetition of ETV; an individual evaluation in all cases is expressly recommended.

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Edited by Bora Gürer

Hydrocephalus is a common manifestation of many diseases. Caring and treating a patient with hydrocephalus involve engagement and acquire a deep knowledge of anatomy, physiology, and technical details. Despite the technological developments, treatment of hydrocephalus is still a challenge for every neurological surgeon.

The aim of this project is to provide a detailed and accessible information for every single discipline, not only for neurological surgeons, involved in the diagnosis and treatment of the patients with hydrocephalus.

Published in London, UK

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ISBN 978-1-83881-438-0