



Endoscopic Treatment of Hydrocephalus Through Endoscopic Third Ventriculostomy

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Contents

Introduction	1
Historical Background	2
Radiological Evaluation of Ventricular Anatomy	3
Neuroendoscopic Instrumentation	6
Optic Devices	6
Camera and Monitor	9
Neuronavigation	10
Indications	11
Pure Obstructive Hydrocephalus	11
Hydrocephalus in Posterior Cranial Fossa Tumors	14
Hydrocephalus with Possible Subarachnoid Spaces Impairment	16
Postinfectious Hydrocephalus	18
Hydrocephalus Associated with Dandy-Walker Syndrome	19
Constrictive Hydrocephalus	20
How to Evaluate the Outcome of ETV	22
Complications	24
Intraoperative Complications	25
Immediate Postoperative Complications	26
Neurological and Endocrinological Morbidity	26
Mortality	27
Conclusion	27
References	28

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Introduction

Endoscopic treatment of hydrocephalus is actually the mainstay of treatment of pure obstructive forms of hydrocephalus; the constantly developing technology and gain of experience has led to extend the number of indications to the use of neuroendoscopic techniques to a variety of hydrocephalus etiologies, as primary procedure (e.g., in hydrocephalus forms with mixed non communicating and communicating etiology) as well as an added procedure to extrathecal shunts to simplify the ventricular anatomy and reduce the number of ventricular catheters and consequently the rate of complications of shunts (e.g., in multiloculated hydrocephalus).

Historical Background

The first application of the concept of visualization of human cavities through natural orifices or small wounds dates back to Bozzini, who carried out the first endoscopic procedure with a series of 45° mirrors lightened by a candle for the study of the urethra and the rectum. A real cornerstone in the history of neuroendoscopy was however represented by the invention of the electricity bulb by Edison in 1879, borrowed the same year by Nitze who adopted it for the construction of the first cystoscope to remove bladder stones.

The development of the computer chip TV camera during the 1980s finally ratified the beginning of the modern endoscopic surgery (Stellato 1992).

The first attempt to use endoscopic instrumentation for the management of hydrocephalus was performed by Lespinasse in 1910, an urologist who used a cystoscope to explore the lateral ventricles of two hydrocephalic children in order to coagulate the choroid plexuses. The experience was repeated few years later by Dandy (1918) who performed the avulsion of choroid plexuses in five children and was to first to use the term “ventriculoscope” that was constituted by a rigid Kelly cystoscope headlighted with the aid of transillumination of the heads of his patients. Dandy was also the first to propose the opening of the third ventricle floor through a subfrontal approach, at the cost of sacrificing one optic nerve (Dandy 1922). One year later, Mixter (1923) synthesized the ideas of Dandy in a single procedure and performed a third-ventriculo-cisternostomy using a urethroscope introduced through the anterior fontanel and a flexible probe in a 9-month-old child with non-communicating hydrocephalus. The presence of contrast dye (previously injected in the lateral ventricle) in the lumbar subarachnoid space demonstrated the success of the first ETV ever realized. Though the procedures were correctly carried out, the following attempts (Putnam 1943) were characterized by unrewarding long-term results and unacceptable morbidity and mortality rates, mostly due to poor design of the instruments and optical apparatus. The interest in neuroendoscopy further declined during the second half of the twentieth century after the introduction of low morbidity/mortality procedures for the implantation of CSF shunting devices.

Several factors have contributed to the renaissance of the neuroendoscopy in the last two decades, the main one remaining the introduction by Harold Hopkins of a

solid-rod lens system during 1960s, which still represents the base of the current nonflexible endoscopes, further enhanced by Guiot who introduced the solid quartz rod lenses, with their internal reflective properties (Guiot 1973). The advent of microsurgery made the neurosurgeons more confident with the neuro-microanatomy and more conscious about the potential applications of the neuroendoscopy. One of the main fields to which the renewed interest was directed was the management of hydrocephalus, seen the perspective possibility that it could represent a valid alternative to the CSF shunt devices and the risks related to their implantation both from an infective and mechanical point of view. The first modern and important clinical experience with ETV was reported by Vries in 1978 (Vries 1978); Jones et al. (1990) reported about the possibility to manage different types of noncommunicating hydrocephalus. Their work became a milestone for the indications and the evaluation of the results after ETV. An increasing number of reports on large series of hydrocephalic patients treated by ETV, which appeared in literature in recent years, justify the increasingly wider use of the technique throughout the world. Many innovative clinical and experimental studies concerning the procedure itself, the instrumentation, and the possible integration with other techniques represent the last steps in the diffusion of ETV (Vandertop et al. 1998; Foroutan et al. 1998; Broggi et al. 2000; Burtscher et al. 2002; Decq et al. 2000; Horowitz et al. 2003).

Thanks to the improvement in the video imaging, neuronavigation, and endoscopic instrumentation, the current use of the neuroendoscope for the management of pediatric patients with hydrocephalus has been extended to also to simplify complex forms of hydrocephalus (aqueductal plasty, septostomy of the septum pellucidum, choroid plexectomy). Advances of three-dimensional imaging, image fusion, surgical armamentarium, and exoscopic surgery have represented a major contribution in this context (Frazee and Shah 1998).

Radiological Evaluation of Ventricular Anatomy

It is almost universally accepted that whenever an ETV procedure is planned a MR study of the brain should be performed. Basic MR studies allow to obtain an overall view of ventricular structures and their anatomical relationships, width of the cerebral mantle, size of the basal subarachnoid spaces, and basilar artery position. Three-dimensional reconstructions and distances measurements can be subsequently obtained and used in the preoperative planning.

In such a regard, previous studies have been almost centered on clearing the anatomical differences induced by an active ventricular dilation and their possible influence on the preoperative planning of the endoscopic procedure. Duffner et al. (2003) compared preoperative MR findings of 30 patients with a diagnosis of obstructive hydrocephalus and 30 healthy volunteers. They found significant anatomic differences between the two groups; in particular lateral ventricles height was 2.08 times higher in the hydrocephalic patients so as third ventricle width (4.39 times larger in the hydrocephalic group). The mean distance between anterior and posterior commissures was 1.19 times longer in patients than in volunteers, and the distance

between the ventricular system and the cortical surface was significantly higher in this latter group; moreover, the mean size of the Monro foramina was about 20 times the size in hydrocephalic patients if compared with normal individuals. The position of an optimally located burr hole for third ventriculostomy was also calculated and was found to vary significantly between different patients. In an anterior-posterior direction, it varied between 16.1 mm in front of and 46.5 mm behind the coronal suture, with a mean value of 8.2 mm behind the coronal suture, that is, about 2 cm posterior to the point suggested by most authors (1 cm. anterior to the coronal suture). The study provided two further interesting conclusions: the first is that a rigid endoscope used for ETV should not exceed an external diameter of 5 mm and the second is that they should be longer than 120 mm to allow a safe access to the floor of the third ventricle (Duffner et al. 2003).

More recently the interest has been redirected to the improvement of anatomical study of CSF pathways as well as to investigate CSF flow, in order to predict the success or failure of a third ventriculostomy. Cine-cardiac gated phase contrast MR has represented the gold standard imaging sequence in this context during the last 15 years. Different anatomical sequences have been added to the available possibilities, which actually can be considered as complimentary for the correct understanding of the pathophysiology of the hydrocephalus, or in a different asset of the success of the endoscopic procedure. Concerning the assessment of the anatomic features of the ventricular system certainly turbo spin-echo (TSE), three-dimensional constructive interference in the steady state images (also known as 3D CISS) represents the most valuable option, being able to clearly define subtle membranes both inside the ventricular system as well as in the subarachnoid spaces. However, these sequences do not allow to have a clear demonstration of the functional status of the ventriculostomy in the follow-up of operated on children. Dincer et al. compared the results of postoperative MRs of 24 children who underwent a clinically successful ETV 1 year after surgery. Cardiac cine-gated phase contrast sequences were able to correctly demonstrate the CSF flow through the stoma in all cases. The predictivity of 3D CISS sequences was only 71%, whereas the sequences that most approached the sensitivity of phase contrast MR were represented by 2 mm sagittal Turbo Spin Echo acquisitions both with and without flow compensation (Dinçer et al. 2011). Magnetic Resonance cisternography has been suggested as a further imaging modality that however should be used only in cases in which the combination of anatomical and functional sequences do not allow to come to definite conclusions (Di et al. 2009).

Alternative anatomical sequences that have demonstrated a reliable role in recent years are represented by fast imaging with steady-state precession (FISP 2D) (Lucic et al. 2014) and 3D-Space, whose reliability to demonstrate preoperatively an obstructive nature of the hydrocephalus has been reported to be as high as 98% in large series (Ucar et al. 2015). Preliminary data also suggest that this imaging modality might give even less ambiguous results than traditional Turbo-Spin Echo sequences in doubtful cases (Ucar et al. 2015; Algin et al. 2015).

In the same ground of comparative flow-anatomic studies, McCOy et al. (2013) explored the relationships between aqueductal flow of cerebrospinal fluid and the

changes of the anatomical configuration of the cerebral aqueduct in a consecutive series of 43 patients. The measured aqueductal cross-sectional area was significantly correlated with MRI CSF flow data based on phase contrast measurements, with a significant prevalence of tubular or trumpet shaped aqueducts in case of non-obstructive forms of hydrocephalus.

Another useful application of 3D MR reconstructions is related with virtual neuroendoscopic procedures. Virtual MR neuroendoscopy has been introduced in the clinical practice in late 1990s. Brutscher and coworkers (Brutscher et al. 1999) produced virtual endoscopic images of 5 nonhydrocephalic brain specimens and compared the obtained images with intraventricular endoscopic views. The foramen of Monro, fornix, choroid plexus, clivus, mammillary bodies, and basilar artery could be virtually visualized, and the images obtained were comparable to the actual views. Similar results were obtained by Auer and Auer (1998), who simulated several approaches to the ventricular system by virtual MR endoscopy in healthy volunteers as well as in patients with hydrocephalus. Rohde et al. (2001) analyzed the sensitivity of virtual MRI endoscopy in detecting anatomic variations that could be found at surgery. Seven anomalies of the normal ventricular anatomy were encountered during ETV in 5 of 18 patients; five of the seven anomalies had been already identified by virtual MR with an overall sensitivity of 71%. All the missed information concerned anatomical variations of the third ventricular floor. This anatomic structure invariably appeared as a defect when it was translucent so as when it was thick and opaque or steeply inclined. According to the authors, the advantage of this virtual endoscopy of the third ventricle region is that the surgeon can “look through” the third ventricular floor onto the first segment of the posterior cerebral arteries and onto the basilar artery tip and relate these data with the planned surgical approach (Rohde et al. 2001). However, other authors have underlined the difficulties to study the anatomic relationships of the basilar bifurcation with the designated site of ventriculostomy due to the lack of segmentation between cerebral vessels and brain tissue (Jodicke et al. 2003). These results have been recently confirmed by Zhao et al. (2015). They compared the results of magnetic resonance virtual endoscopy with ventriculoscopy findings in 15 pediatric patients with hydrocephalus and were able to achieve similar results as ventriculoscopy in demonstrating the morphology of ventricular wall or intracavity lesion. In addition, MRVE was able to give a virtual vision of the lesion from distal end of obstruction, as well as other areas inaccessible to ventriculoscopy.

Alternative devices for virtual neuroendoscopy have been proposed such as 3D ultrasonography (3D-US). Jodicke et al. (2003) evaluated the sensitivity of 3D US-based virtual neuroendoscopy in the identification of parenchymal and vascular anatomical landmarks of the third ventricle. In the authors' experience, the definition of ventricular and vascular structures position was comparable to virtual MR neuroendoscopy. One main advantage of 3D US-based over MR virtual neuroendoscopy was the co-registration of parenchymal ventricular and vascular anatomy at one single image acquisition due to flow detection and coding using the sensitive Doppler properties of ultrasonography. On the other side reflexion artifacts

hamper the correct view of the basal cisterns, due to the artifacts coming from the proximity of the bony clivus.

Neuroendoscopic Instrumentation

Optic Devices

The endoscopes specifically designed for neuroendoscopy can be classified into four types:

- Flexible fiberscopes
- Steerable fiberscopes
- Rigid fiberscopes
- Rigid rod lens endoscopes
- Videoscopes

These endoscopes vary for diameter, optical quality, number, and diameter of working channels.

Flexible Fiberscopes

These endoscopes are not useful for third ventriculostomy. They have a very small diameter (<2 mm), which allow their use inside the lumen of ventricular catheters for optimal ventricular catheter positioning during ventriculoperitoneal shunting. Their limitations are poor quality of vision and the absence of a working channel.

Steerable, Flexible Fiberscopes

Flexible-steerable endoscopes became a reality in the late 1990s with the development of fiber optic technology (Fukushima et al. 1973; Hecht 1999). They are constructed of silica glass (which can be flexed without breaking) (Nobles 1998). The image formed by the objective lens is relayed to the eye lens by multiple fibers contained in a very small package.

The main characteristic of the flexible and steerable fiberscope is that the last 4 cm can be oriented 100° upward and 160° downward, allowing to look and work around the corner. The diameter of the scope ranges from 2.3 to 4.6 mm, with the potential to be used also in patients with small ventricles and a small foramen of Monro. The size of the device usually determines the number of individual fibers, consequently the number of pixels: the smaller the size, the fewer the number of pixels (Nobles 1998). The diameter of the working channel ranges from 1.0 to 1.5 mm, allowing the introduction of 3-French (1 mm) flexible instruments (microscissors, micrograsping forceps, microbiopsy forceps, monopolar electrodes, Fogarty balloon). Distinct irrigation channel and the outflow channel are usually available. Access to the ventricle is possible using a dedicated peel-away sheath. Some steerable scopes with only one working channel present the limit of very slow irrigation when the instrument occupies the channel. For this reason, it is impossible to work under

continuous irrigation and this makes more complex operations (tumor biopsies or removal) more complicated. When an instrument is introduced into the working channel, the steering properties are decreased, sometimes significantly, according to the stiffness of the instrument introduced. The steerable scope modifies the orientation of the optical fibers but also of the working channel, allowing the instruments to reach all the structures visualized. Some steerable scopes cannot be sterilized according to the protocols used in some countries (i.e., France) in order to prevent prion transmission. These protocols include decontamination with alkaline medium and sterilization for 20 min at 134°. Therefore, these devices should be considered as disposable, which makes their use prohibitive in these countries.

Rigid Fiberscopes

These fiberscopes are formed by a main rigid body of variable length (13–27 cm) with a diameter of 3–4 mm. This contains the end of the optic fiber tract, a working channel (1–2 mm), and the irrigation-aspiration channel. Separate inflow and outflow channels avoid excessive increase of ICP balancing irrigation with outflow. Access to the ventricle is possible using a dedicated peel-away sheath. The major advantage is that this endoscope is extremely light and short and can be handled like a pencil, so that it is easier to manipulate. The camera and the light source can be positioned as far as 40 cm away on the operating table. One single soft, fiberoptic cable is the only link to the fiberscope itself. The small diameter of the scope allows its use in neonates and in case of small ventricles – small foramen of Monro. Vision is superior to that with the steerable fiberscopes because the number of optic fibers can be higher since there is no need for tip orientation. However, to obtain good quality video image when using fiberoptic endoscopes, one must choose a magnification on video screen that does not displace the spaces between the pixels and even with an endoscope of 10,000 pixels, it is not possible to achieve an image magnified greater than 8 inches an issue which significantly limits the image quality of these instruments. For this reason, due also to the development of lighter rigid lens endoscopes, rigid fiberscopes have been substantially abandoned in most of the centers performing high volumes of patients with a surgical indication to ventricular endoscopy.

Rigid Rod Lens Endoscopes

The quality of vision is the main advantage that makes the rigid rod lens scope an indispensable item in the basic armamentarium for ventricular neuroendoscopic procedures. The actual rigid lens endoscopes still follow the Hopkins rule, since 1960. The revolutionary concept proposed by Hopkins was to increase the quality of images through a system composed by a series of glass rods with small air gaps, the exact opposite of the design since then used. Further reduction in light loss is achieved through the coating of the glass surfaces with an ultrathin layer of magnesium fluoride. This layer markedly decreases the reflection and improves the optic characteristics of endoscopes and cameras (Nobles 1998; Shiau and King 1998; Siomin and Constantini 2004). With this technology, the quality of vision is extremely sharp and allows easier and more precise identification of the anatomical

structures encountered, with an excellent visual definition of details. The rod lens system requires the presence of the camera and of the fiberoptic cable for the cold light attached to the proximal extremity of the endoscope. One of the relative disadvantages of rigid lens systems is that they only allow targets to be reached on a straight line from the burr hole; from an operative point of view, it also requires the presence of an endoscope trochar with multiple parallel operative channels: the optic is inserted in the “optic channel,” whereas the instruments are inserted in different operating channels.

The trochars are of different diameters, according to the number of channels available. For third ventriculostomy, four channels should be available: an optic channel (in which the optic is inserted), a working channel for surgical instruments, an irrigation channel, and an overflow channel. The diameter of the whole system ranges from 3.2 to 6 mm, and the working channel allows the use of 2 mm instruments. However also “miniature endoscopes” (3.2-mm outer diameter) have been developed for use in pediatric patients (4.0-mm Gaab II miniature system, Karl Storz GmbH & Co., Tuttlingen, Germany). In some endoscopes (Minop System, Aesculap, Tuttlingen, Germany), 1 mm instruments can be introduced short term through the irrigation channel for bi-instrumental operation. Decq endoscope (Karl Storz GmbH & Co., Tuttlingen, Germany) is the only system provided by two working channels of 2 mm. Larger throcar sheaths have been specifically developed for tumor or cyst surgery, the two working channels diameters ranging from 3.5 and 4.0 mm \times 5.2 and 7.0 mm. This is specifically designed for tumor or cyst surgery allowing simultaneous grasping and fenestration (or aspiration). Angle of view of the endoscope can range from 0° to 120°, according to the objective lens used. The most used are 0° and 30°. The 0° objective portrays only what it is viewing head-on, minimizing the risk of disorientation (Siomin and Constantini 2004). The 30° objective offers some advantages (Decq 2004): by simple rotation it provides an angle of view with a surface area twice as large as that obtained with 0° objective, and it allows a better control of the instruments because with the 30° objective the instruments introduced in the working channel (parallel to the endoscope) converge towards the center of the image (directed at 30°), while with the 0° objective the instruments remain in the periphery of the image. More than 30° angled objective are useful only to “look around the corner” (Decq 2004).

Videoscope

A videoscope is characterized by a 1 CCD chip camera positioned at the proximal tip of the endoscope. This allows for the extreme simplification of the optical system, without the need for complex and long rod lenses systems improving at the same time significantly the quality of vision if compared to the fiberscopes. Although the 1 CCD camera is somehow less performant than the 3 CCD camera that can be used with rigid rod lenses systems and fiberscopes, the proximity of the camera to the target of vision allows for excellent magnification and sharpness of the image. Moreover, the steerable properties of the device are preserved because of the lack of rigid lens systems. Videoscopes have been originally designed for ENT use, with an outer diameter of 6–8 mm; videoscopes with smaller outer diameter for

neuroendoscopic use are actually available only in Japan (Kamikawa et al. 2001a; Kamikawa et al. 2001b; Tamura et al. 2013). The real, significant advantage of this device is the excellent quality of vision (1 CCD camera like), comparable to the 1 CCD rod lens systems, associated with the steerable properties, allowing for perfect fusion of rigid and steerable systems. Moreover, this system has the advantage to be combined with Narrow Band Imaging filters for the more correct definition of the most vascularized tumor areas. Sasakawa et al. (2014) performed an endoscopic biopsy in 14 patients using the combination of the videoscope and of the NBI filter. Flexibility of the instrument and quality of the intraoperative images were confirmed, together with a significantly increased vascularity of specimens who appeared as cyan in color under NBI, compared with regions that appeared normal in color using this kind of filter. A further development of videoscopes is represented by the videoendoscope (digiCAMeleon, Karl Storz GmbH, Tuttlingen, Germany) all in one system with 1 sensor and an internal LED light source. The device offers a resolution of 1920×1080 pixels and weighs approximately 215 g. It offers a digital, continuously changing direction of view (DOV), i.e., between 0 and 70 degrees, and is equipped with an autorotation and offset mode, offering a resolution of 1920×1080 pixels and weighing only 215 g. The main advantages of the new system include improved maneuverability of the scope on account of reduced bulk and integration of the camera and fiberoptic light components (Cavallo et al. 2016).

Camera and Monitor

The camera is one of the most critical components of the endoscopy system. Actually all the cameras are built with a chip concept. The chip technology is based on the presence of horizontal and vertical photosensitive elements (lines); the points of intersections correspond to pixels. When light hits one of these pixels, an electric current is generated: the brighter the light, the higher the voltage. A digital image is created according to the current voltage generated at the horizontal and vertical matrix of the camera and is stored in the memory of the camera (Nobles 1998; Siomin and Constantini 2004).

Up to 10 years ago the two most common used cameras included: a single chip charged coupled device (CCD) and a three chip CCD. A good resolution for neuroendoscopy is available with 0.5 inches single chip cameras (resolution of 500 lines) (Woo 2016). If the resolution is poor, the image needs computer-enhancement. The three chip CCD produces images of better quality (more than 800 horizontal lines) but is more expensive and heavier. So most endoscopic system uses single chip cameras. Some manufacturers produce both the types of digital cameras (David 1 and David 3, Aesculap, Tuttlingen, Germany; Image 1 and Image 3, Karl Storz GmbH & Co., Tuttlingen, Germany). In some models all the function can be controlled by the surgeon in the operative field. Zoom endo-lens is useful to enlarge the image section.

An evolution of both camera types has been the development of HD cameras able to acquire with a definition of up to 1080 lines with the same basic concept, actually the most extensively available system. Improved resolution and color information are the main advantages of HD imaging. Additionally, because of the 16:9 aspect ratio, the viewing field of the HD camera is larger than with the 4:3 aspect ratio of the SD camera. The progressive image processing of the HD camera provides a much clearer image than the interlaced image processing of the SD camera, especially with a modern flat panel screen. Further developments have been represented by 4 K cameras connected to 4 K videos which have a 3840×2160 pixels, which, though increasing furtherly the definition of image view, have the disadvantage of heavy video recordings, which are more difficult to manage with the actually available PC video managing software (Woo 2016).

Neuronavigation

Frameless neuronavigation is actually commonly used for ventricular endoscopic procedures (Broggi et al. 2000; Alberti et al. 2001; Hopf et al. 1999a; Riegel et al. 2000, 2001, 2002; Schroeder and Gaab 1999; Tirakotai et al. 2004). It is able to determine the optimal entry point and to plan the exact trajectory to the lesion. It is also useful for intraoperative orientation, especially in cases of impaired visualization, distorted anatomy, or narrowed ventricles (Tirakotai et al. 2004). In endoscopic third ventriculostomy, the use of neuronavigation may not be necessary (Schroeder and Gaab 1999); however, in cases with thickened, nontranslucent third ventricular floors, neuronavigation is useful for anatomical orientation (Alberti et al. 2001; Tirakotai et al. 2004). As discussed by Tirakotai et al. (2004), brain shift can be a major factor in influencing the accuracy of the target localization. This problem occurs less often if some precautions are taken to prevent the abrupt change of CSF compartments or cystic lesion. The position of the burr hole should be at the highest point in order to minimize CSF loss. Moreover, brain distortion occurs rarely in midline structures and most endoscopic procedures use midline structures as anatomical landmarks (Tirakotai et al. 2004).

The development in the first decade of 2000 of magnetic neuronavigation has further improved the possibilities to take advantage from neuronavigation systems, which actually are commonly used also in smaller babies, due to the absence of any need for head fixation. With these systems, patients can be registered for navigation by surface rendering in the supine position. After confirming accuracy, they can be repositioned for endoscopic surgery with the head fixed slightly on a horseshoe headholder. EM navigation might then be performed using a flexible stylet introduced into the working channel of a rigid endoscope.

Indications

A correct clinical indication is the most important factor influencing the success rate of endoscopic third ventriculostomy (ETV). Advances in magnetic resonance (MR) imaging have improved the understanding of the specific physiopathologic mechanism at the base of the different forms of hydrocephalus consequently representing an essential adjunct for the correct patient selection. A more accurate preoperative diagnosis of mixed types of communicating hydrocephalus, where obstructive factors may still play a role, has led to extend the indications for ETV to patients, once excluded, namely, subjects with posthemorrhagic hydrocephalus, postinfectious hydrocephalus, and hydrocephalus in myelomeningocele.

Pure Obstructive Hydrocephalus

Results of ETV in Patients with Primary and Secondary Aqueductal Stenosis

Aqueductal stenosis is considered the ideal indication for third ventriculostomy. When patients with an exclusively obstructive triventricular hydrocephalus are selected, the success rate is quite homogeneous and stable, being between 63% and 92% in most series (Böschert et al. 2003; Gangemi et al. 2007; de Ribaupierre et al. 2007; Spennato et al. 2013; Salvador et al. 2014; Durnford et al. 2011). The influence of age on the final result has been long discussed. Jones et al. (1994) reported a 40% success rate of ventriculostomy in children with triventricular hydrocephalus operated within the age of 2 years. For the same pathology with a clinical onset within the age of 2 years, but operated on later in childhood and adolescence, the success rate increased to 71%. Kim et al. (2000) reported age as a significant predictor of outcome. Of the six patients younger than 1 year of age, only two (33.3%) had good outcomes, whereas 19 out of 23 patients older than 1 year of age (82.6%) were successfully treated with ETV. Similar results were reported by Grunert et al. (2003): in their personal experience a statistically worse success rate was found in infants (22.3%) if compared with children aged over 1 year (71.4%) and adults (81.6%). More recently Sacko et al., (2010) reported that infants less than 6 months of age had a 5 fold increased risk of ETV failure compared with their older counterpart. Ogiwara et al. further divided children in the first 6 months of life in two groups reporting a 25% success rate of ETV in patients younger than 3 months of age, which raised to 45.5% in patients from 3 to 6 months of age (Ogiwara et al. 2010).

On the contrary Sufianov et al. (2010) reported a clinical and radiological success of ETV in 30 (71.4%) of 42 procedures performed in infants during a mean (\pm SD) follow-up period of 45.0 ± 4.8 months (range 12–127). A negative relationship was found between success of ETV and the thickness of the floor of the third ventricle (the most effective procedures were those in which the floor of the ventricle was thinnest [$p < 0.05$]). There was a highly significant correlation between ETV success and prolapse of the ventricle floor ($p < 0.001$). Also, there was an inverse

relationship between ventricle floor thickness and the width of the third ventricle ($p < 0.005$). Finally there was significant correlation between ETV success and patient age at onset of hydrocephalus (the most effective procedures were in patients in whom signs of hydrocephalus first occurred after 1 month of age [$p = 0.02$]).

The above cited and continued discussion led in the middle of the first decade of 2000 to start a multicenter study in order to collect a large number of infants (<24 months old) affected by triventricular hydrocephalus due to aqueductal stenosis. Recruitment started in 2004 with a cohort design, which contained both a randomized and a nonrandomized arm. Patients received either an ETV or shunt, based on randomization or parental preference. Patients were followed prospectively for time to treatment failure, defined as the need for repeat CSF diversion procedure (shunt or ETV) or death due to hydrocephalus. Survival analysis was used to compare time to failure for ETV versus shunt. A total of 158 patients met eligibility criteria (median age at surgery 3.6 months, IQR 1.6–6.6 months) across 27 centers in 4 continents. Since only 52 patients (32.9%) were randomized, all 158 patients were analyzed together (115 ETV, 43 shunt). Actuarial success rates for ETV vs. shunt at 3, 6, and 12 months were as follows: 68% vs. 95%, 66% vs. 88%, and 66% vs. 83%. The 6-month ETV success rate of 66% was slightly higher than would have been predicted by the ETV Success Score (57%). The hazard ratio for time to treatment failure favored shunt over ETV (3.17, 95% CI 1.45–6.96, $p = 0.004$), after adjusting for age at surgery, history of previous hemorrhage or infection, continent, and randomization status. Patients younger than 6 months of age appeared to do relatively worse with ETV than older patients. An important primary outcome of health status will complete the study when all patients will have reached 5 years of age with a complete neurocognitive evaluation (Kulkarni et al. 2016a).

Incomplete development of the subarachnoid spaces and consequent impairment of CSF absorption are the main factors which are claimed to explain why ETV fails more frequently in infants (Kim et al. 2000; Buxton et al. 1998a; b; Hopf et al. 1999b; Gallo et al. 2010). However, considering exclusively children with pure obstructive hydrocephalus, other factors might have influenced the reported ETV failure rate in infants. First of all in most of these series a second endoscopic view was never or not always performed, in order to establish ventriculostomy patency, and this factor might further have negatively influenced the overall outcome. In a multicenter study, Siomin et al. reported repeat ETV as effective as primary procedures with an overall 65% success rate (Siomin et al. 2001). Javadpour et al. (2003) analyzed the ETV success rate in a series of 21 infants with obstructive hydrocephalus. The success rate in 7 infants with congenital aqueductal stenosis was 71%; a redo third ventriculostomy was performed with success in one of the two initial failures with a final success rate of 86%. Wagner and Koch (2004) confirmed this finding, reporting the occlusion of the ventriculostomy site as the most frequent factor causing ETV failure in infants. The lower ICP with slowing of CSF flow through the stoma might explain ventriculostomy obstruction in this subset of patients (Böschert et al. 2003).

Another important point to consider is the time for defining ETV failure. According to Beems (Beems and Grotenhuis 2002), infants have a longer adaptation

time if compared with their older counterpart. Forty-five percent of the 35 patients, aged less than 2 years, who underwent successful ETV at their institution required a relatively long adaptation time (mean adaptation time: 1 week). This is important to recognize, because it means that these young patients should not be treated too soon using a shunting device if the ETV does not lead to immediate relief of the symptoms.

A further discussed point is the influence of AS etiology on the success rate of ETV procedures. Most authors report ETV as effective in primary as in secondary forms of aqueductal stenosis (Böschert et al. 2003; Hopf et al. 1999b; Fukuhara et al. 2000, 2002; Rieger et al. 2000; Oppido et al. 2011; Roth and Constantini 2015). Pople et al. (2001) reported ETV to be effective in the control of the hydrocephalus in 17 out of 18 cases with pineal region tumors. Macarthur et al. (2001) referred a long-term (median follow-up: 12 months) control of the hydrocephalus in 39 out of 47 pediatric patients (82.9%) with secondary neoplastic AS. Similar results were reported by Rieger et al. (2000) in a series of 7 patients with pineal region tumors. A successful control of the hydrocephalus was obtained in all cases; however, six of the seven children also underwent tumor removal few days after the neuroendoscopic procedure, this factor possibly contributing to the long term results. In the more recent series by Diaz et al. (2014), eleven patients affected by obstructive hydrocephalus due to a tectal plate glioma had ETV as a primary procedure and three patients underwent ETV as a substitute for shunt revision at the time of shunt failure. At follow-up (median 3.9 years, range: 2.2–7 years), 13 of 14 patients were shunt independent with excellent ($n = 9$) or good outcomes ($n = 5$).

In contrast with what previously said, Goh and Abbott (2000) recently reported a 49% failure rate of ETV in 63 patients with tumoral AS (mean follow-up 11.4 months). This result compared unfavorably with their 65% success rate obtained in children with primary aqueductal stenosis. An analysis of the different series does not seem to show differences in the prevalence of tumor location. Nevertheless none of the reported authors details histological types nor the presence or absence of subarachnoid tumor seeding, a factor which might specifically influence the success of ventriculocisternostomy. This is particularly true for some pineal region tumors (i.e., germinal cell tumors), and it is confirmed by the fact that when exclusively benign lesions are selected (i.e., tectal plate gliomas), the success rates of ETV are almost homogeneous (ranging between 65% and 100%) and comparable with those obtained in patients with primary AS (Macarthur et al. 2001; Grunert et al. 1994). Moreover, as part of the therapeutic protocol, endoscopic tumor biopsy was combined with ETV in selected cases of some of these series; either minor intraoperative bleeding and/or increase in CSF proteins which can follow the bioptic step of endoscopic surgical procedures may condition the functional patency of the ventriculostomy site.

Another point that has been investigated in recent years is the role of ETV as secondary procedure in children with AS and previously implanted malfunctioning or infected shunt. Most series report results comparable to those obtained in primary procedures with overall success rates ranging from 62.9% to 82.3% (Böschert et al. 2003; Cinalli et al. 2004a; Marton et al. 2010). The relative variability of these

results can again be ascribed to different selection criteria and different methods in the evaluation of results. Boschert et al. (2003) found that two of the three failures in their seventeen patients series occurred in children with shunt malfunction and a previous history of shunt infection, suggesting a concurrent CSF absorption impairment in the pathogenesis of the hydrocephalus for these cases. However, other authors have pointed out that previous shunt infections or infected shunt malfunctions do not influence outcome. Jones et al. (1994) reported on 4 patients having ETV for AS and infected shunt malfunction having a 75% success rate; Buxton et al. (2003) referred that 33% of their 88 patients had previously suffered one or more shunt infection, but they did not observe significant differences in their outcome if compared with those who did not have a history of an infected shunt.

Regarding evaluation of results, Cinalli et al. (1998) reported 30 patients, having a 76.7% ETV success rate, but many patients in their series were left with a potentially patent shunt in situ; only seven patients were left in the initial stages to rely on the NTV alone (6 with their shunts removed and one with it clipped). More stringent criteria were used by Buxton et al. (2003) who retrospectively analyzed a personal series of 27 children with AS who underwent secondary third ventriculostomy at their institution. The shunt was removed or tied off in the neck in all cases; the final success rate was 62.9%.

Hydrocephalus in Posterior Cranial Fossa Tumors

The incidence of preoperative hydrocephalus in children with posterior fossa tumors is around 60–80%; however, only 15–25% of these patients require a permanent “shunting” procedure. Younger age, the severity of hydrocephalus at diagnosis, midline tumor localization, rate of tumor removal, and the use of substitute dural grafts are all factors considered to increase this risk (Sainte-Rose et al. 2001).

Different protocols have been proposed for the management of hydrocephalus in children with posterior fossa tumors. Actually most pediatric neurosurgeons use a combination of corticosteroids, early tumor surgery, and external ventricular drainage where needed (Fritsch et al. 2004; Sainte-Rose 2004). Children with persistent postoperative hydrocephalus can be alternatively treated with ETV or shunt implantation. An important drawback of this protocol is the 5–10% risk of CSF infections which is related with external ventricular drainage positioning (Rappaport and Shalit 1989); upward brainstem herniation and intracranial hemorrhages have been also described.

The role of ETV in the management of persistent hydrocephalus after posterior fossa tumor surgery is discussed. Jones et al. (1990) reported postoperative ETV to be successful in one of two patients, the second procedure being technically impossible to perform due to hemorrhage. Sainte-Rose et al. (2001) performed ETV in 8 patients after posterior fossa surgery and in further three previously shunted children as secondary procedure, with an overall success rate of 100%. A lower success rate was reported by Ruggiero et al. (2004), ETV failing in 2 out of four postoperatively treated children. In a previous experience from our Institution, thirty

on a total of 104 children (28.8%) operated on between January 2001 and February 2007 for a posterior fossa tumor needed a further surgical treatment for the persistence of the hydrocephalus after tumor removal. ETV was overall successful in 90.0% of the patients (Tamburrini et al. 2008).

An alternative management strategy was proposed at the beginning of 2000 by Sainte-Rose et al. (2001). Sixty-seven patients affected by posterior fossa tumors and hydrocephalus underwent endoscopic third ventriculostomy prior to tumor removal; postoperatively four of them (6%) required a second shunting procedure. A comparable group of 82 children underwent tumor removal as first surgical step; the rate of postoperative hydrocephalus in this subset of patients was 26.8%, significantly higher than in the first group ($p = 0.001$). However, the same authors acknowledged that the routine application of preoperative third ventriculostomy results in a proportion of patients undergoing an “unnecessary” procedure. Overall the “shunting” rate in their preoperative ventriculostomy group was 106%. Moreover, though it was not the authors’ experience, the tumor bulk may cause a forward displacement of the brainstem reducing the space for ventriculostomy with an increased operative risk. After tumor removal, the physiological subarachnoid hemorrhage may alter CSF dynamics increasing the risks of secondary subarachnoid membranes development and third ventriculostomy obstruction. The risk of ETV obstruction after tumor removal is conditioned by the operative position of the patient for removing the tumor, being higher in children operated on in prone position (Tamburrini et al. 2015). Finally the role of preoperative ETV in “preventing” postoperative hydrocephalus has not been confirmed in other series. Ruggiero et al. (2004) preoperatively performed ETV in 20 children with posterior fossa tumors. One of the procedures was complicated by intraventricular bleeding requiring an external ventricular drainage and subsequent VP shunt implantation. Three of the remaining 19 patients developed postoperative hydrocephalus with a final 20% postoperative shunting rate. This percentage was comparable in their experience with the 15% rate of persistent hydrocephalus in children who underwent tumor removal as first surgical step. Similar perplexities come from the analysis of more recent series, in which the primary success rate of the procedure has been reported to be between 50% and 85% (Bhatia et al. 2009; El Beltagy et al. 2010). It should also be noticed that performing an ETV instead of implanting a VP shunt for the management of hydrocephalus in children with posterior fossa tumors at diagnosis does not eliminate the risk of complications related to shunts such as intratumoral hemorrhage or upward transtentorial herniation. El Gandour et al. analyzed the records of 53 children with a midline posterior fossa tumor (32 medulloblastomas and 21 ependymomas) associated with marked hydrocephalus at diagnosis and compared the results of preoperative ETV, performed in 32 children with the ones of VPS, that was the management option, before tumor removal, in 21 cases. Intraoperative bleeding occurred in 2/32 children (6.2%) undergoing ETV, one child developing a CSF fistula (2/21 cases: 3.1%). Two of the children who underwent VPS implantation (2/21 = 9.4%) had a shunt infection and one of them died 4.5 months after surgery. Subdural collection occurred in two cases (9.4%), epidural hematoma in one case (4.7%), and upward brain herniation in one case

(4.7%) (El-Ghandour 2011). Similarly, El Gaidi et al. reviewed the medical records of 437 children admitted at their institution with a diagnosis of posterior fossa tumor between across 8 years. Seven children developed neurological deterioration following CSF diversion due to infratentorial complications, consisting in intratumoral hemorrhage (ITH) in 5 cases, and upward transtentorial herniation (UTH), as evidenced by obliteration of the quadrigeminal and ambient cisterns in 2 cases. The overall incidence of complications among the two procedures was 2.8% vs. 1.1%, not significantly different, with a higher risk for large tumors closely extending to the tentorial incisura, especially if severe hydrocephalus and peritumoral edema were present (El-Gaidi et al. 2015).

Hydrocephalus with Possible Subarachnoid Spaces Impairment

Posthemorrhagic Hydrocephalus of Premature Infants

The main pathogenetic factor for the development of posthemorrhagic hydrocephalus is represented by the breakdown of blood products and cellular debris within the ventricular system, which in turn cause chemical arachnoiditis and a fibrotic reaction within the ventricles and the arachnoid granulations, leading to granular ependymitis and adhesive arachnoiditis (Hill and Volpe 1981). However, in some instances infants with intraventricular hemorrhages develop a purely triventricular hydrocephalus (Beni-Adani et al. 2004). An evolutionary mechanism has been suggested for cases initially presenting with an apparently communicating hydrocephalus, and hence primarily shunted, who underwent a successful third ventriculostomy at the time of shunt malfunction. In these specific cases, a reopening of subarachnoid spaces may occur as a consequence of the reabsorption of subarachnoid blood debris, so that, at the time ETV is performed, the access to previously impaired CSF absorption spaces can be obtained, by-passing a persistent obstruction at the level of the Sylvian aqueduct and/or the IV ventricle outlets (Siomin et al. 2002; Smyth et al. 2003).

In the past a history of hemorrhage was considered as a contraindication for ETV, because most patients were considered to suffer a communicating form of hydrocephalus. With the extension of the indications, an increasing number of patients with hydrocephalus and a history of ventricular hemorrhage has been included in ETV management protocols. Siomin et al. (2002) reported the results of a multicentric retrospective study on the role of ETV in children with posthemorrhagic and postinfectious hydrocephalus. Overall 36 children suffered a history of hemorrhage with an ETV success rate of 55.6%. A striking difference was documented between primary and secondary ETV procedures. At a mean follow-up of 1.87 ± 1.6 years, the 13 posthemorrhagic patients who had primarily received a VP shunt had a 100% ETV success rate. On the other hand, all the premature infants in whom ETV was performed as first line of treatment subsequently required a shunt. This result is confirmed by other authors. Buxton et al. (1998a) reported on 16 infants (mean corrected age: 8.9 months) with posthemorrhagic hydrocephalus who all underwent ETV as primary treatment for their hydrocephalus with a success rate of 30%;

similarly Smyth et al. (2003) described a 71.4% success rate in 7 children (mean age: 9.2), all the successes being documented after secondary ETV procedures.

Javadpour et al. (2001) suggested that a further mechanism which may negatively influence the results of ETV in infants with posthemorrhagic hydrocephalus is their low intracranial pressure; ICP compensating mechanisms due to expanding opened sutures may impair to build up a sufficient pressure gradient across the stoma and the arachnoid granulations, with secondary insufficient CSF reabsorption and ventriculostomy closure. In their experience, only three out of ten infants were successfully treated with ETV, two of them requiring two endoscopic procedures, because of first closure of the ventriculostomy.

Two further factors that influenced the outcome of infants who had undergone ETV in the multicentric study of Siomin et al. (2002) were a history of associated CSF infection (the overall ETV success rate in this specific subset of patients was 10%) and the time interval between the onset of hydrocephalus and ETV (mean temporal gap of 6.34 ± 8.31 years successful results versus 3.15 ± 5.16 years for treatment failures). The latter factor probably influenced the results obtained by Beems and Grotenhuis too (Beems and Grotenhuis 2002). In contrast with previous reports, these authors did not find significant difference between the results of primary (44.4%) and secondary (50%) ETV procedures; however, the time interval from the hydrocephalus clinical appearance and the surgical operation was less than 2 years in the children who required a second procedure subsequently. Algorithms intended to improve these results have been proposed. Peretta et al. (2007), reported about 18 consecutive premature patients affected by intraventricular hemorrhage (IVH) grades II to IV, presenting with progressive ventricular dilatation, who underwent the positioning of an intraventricular catheter connected with a subcutaneous Ommaya reservoir. Cerebrospinal fluid was intermittently aspirated percutaneously by the reservoir according with the clinical requirements and the echographic follow-up. The patients who presented a progression of the ventricular dilatation were finally operated for VP shunt implant or ETV according with the MRI findings. Out of the 17 survivors, 3 did not develop progressive ventricular dilatation, and their reservoir was removed; 14 developed progressive hydrocephalus, 5 of whom were implanted with a VP shunt and 9 received an ETV. Secondary ETV was successfully performed in two further shunted children at the time of shunt malfunction, whereas among the nine patients who received a primary ETV, five had to be re-operated for VP shunt implant because of increasing ventricular dilatation. At the end of the follow-up period, 10 out of 17 children affected by posthemorrhagic hydrocephalus in prematurity, a traditionally shunt-dependent condition, were shunt free (59%). One further attempt to improve the success rate of ETV in infants with posthemorrhagic hydrocephalus has been the addition to ETV of choroid plexus coagulation. In a preliminary series of ten patients (four grade III and six grade IV intraventricular hemorrhage), Warf et al. (2011) reported a success rate of the procedure of 40%, the main negative prognostic factor being represented by the presence of arachnoid cisterns scarring. In a subsequent larger series of 25 infants, the same author reported a success rate of 55%, again cisterns scarring are presenting

a main limiting factor for the success rate of the procedure joint with previous shunt placement (Stone and Warf 2014).

Postinfectious Hydrocephalus

In the past postinfectious hydrocephalus was commonly considered as a communicating form of hydrocephalus, the predominant pathogenetic factor being the inflammatory obstruction of the basal cisterns, and cerebral vault subarachnoid spaces. The progressing knowledge of pathophysiology in different CNS infectious diseases has led to a reevaluation of this clinical entity that should actually be regarded as a complex disease.

Results of ETV in Infants and Children with Postinfectious Hydrocephalus

A relatively low number of cases of infants and children with postinfectious hydrocephalus treated with ETV was reported in literature, mostly as a subgroup of combined series. In the multicentric study of Siomin et al. (2002), children with a history of meningitis, ventriculitis, or shunt infection represented only 2.1% (27 cases) of all third ventriculostomies performed in seven international neurosurgical centers; at a mean follow-up of 1.87 ± 1.6 years, the rate of success was 55.6% (15 cases). The severity of the infection, the number of episodes (less or more than 2), location of the inflammatory process (meninges, ventricular system, CSF shunt device), or the type of the agent (bacterial, yeast, unknown culture) did not appear to affect outcome with statistical significance. On the contrary a history of associated hemorrhage had a negative predictive impact (ETV success rate: 10%); actually, at a review of endoscopic video recordings in this last subgroup of patients demonstrated a high incidence (53.8%) of interpeduncular fossa adhesions, a factor which might have accounted for the failure of the procedure at least in some patients.

Age was a significant factor with regards to the outcome, younger patients showing a greater rate of treatment failures. This observation was confirmed in other series and has a particular significance in infants; when patients under 2 years of age are selectively considered, the reported ETV success rate ranges between 0% and 59% (Fukuhara et al. 2000; Siomin et al. 2002; Smyth et al. 2003; Warf 2005a). The role of the age factor is further supported by the relatively high success rate reported, on the contrary, for secondary ETV procedures. For example, Smyth et al. (2003) obtained a 60% success rate in five cases of postinfective hydrocephalus, three of them primarily shunted and then treated by ETV at the time of shunt malfunction. Similarly to what propounded in cases of post-hemorrhagic hydrocephalus, also in postinfectious hydrocephalus the resolution of the acute inflammatory reaction and the temporary control of CSF dynamics assured by the presence of an extrathecal CSF shunt may allow an improvement of CSF absorption mechanisms with time. ETV would then enhance the CSF access to the subarachnoid spaces by-passing a possible persistent obstruction at the level of the aqueduct or fourth ventricle outlets (Siomin et al. 2002; Smyth et al. 2003). The main

attempt to increase the success rate of endoscopic third ventriculostomy (ETV) in infants with postinfectious hydrocephalus has been to combine ETV itself with choroid plexus coagulation. Warf (2005b) referred about a total of 710 children who underwent ventriculoscopy as candidates for ETV as the primary treatment for hydrocephalus. The ETV was accomplished in 550 children: 266 underwent a combined ETV-CPC procedure and 284 underwent ETV alone. A total of 320 infants of this group were affected by postinfectious hydrocephalus. In this specific subset of infants ETV associated with choroid plexus coagulation was successful in 62% of the cases, whereas the success rate of ETV alone was 52%. Although the difference was not significant ($p = 0.1607$), a benefit was not statistically ruled out (power = 0.3). The same authors subsequently validated the results of the comparison among ETV and ETV with choroid plexus cauterization developing a success score adapted to the African population in which the procedure was performed. The variables that were considered beyond age less and above than 6 months were represented by etiology (divided as postinfectious, MMC and other) and by if choroid plexus cauterization was performed unilaterally, bilaterally or not performed at all. Considering only infants with postinfectious hydrocephalus, the probability of success of an endoscopic third ventriculostomy was significantly affected by the addition and completeness of choroid plexus coagulation, ranging from 10% to 15% when ETV was performed alone to 30% when unilateral choroid plexus coagulation was performed, up to 60% when the coagulation of the choroid plexus was bilateral and complete (Warf et al. 2010).

Hydrocephalus Associated with Dandy-Walker Syndrome

Due to the relative rarity of the disease, the papers that can be found in the literature on this subject are essentially limited to case reports or description of very limited series of patients. Hirsch et al. (1984) and Hoffman et al. (1980) reported a 50% success rate (2 out of four patients joining the two series). All the endoscopic procedures were performed under an exclusively radioscopic control, a factor which might have influenced the correct conclusion of the procedure. More recently, a higher success rate was reported by Cinalli (1999) who described three long-term outcomes out of four personal cases.

In children with secondary aqueductal stenosis, a combined ETV and aqueductal stenting placement has been suggested. Mohanty (2003) successfully performed this kind of procedure in two out of three patients (66.6%). Intraoperative endoscopic confirmation of aqueduct patency might be useful in order to select the appropriate surgical procedure (Jodicke et al. 2003). The meta-analysis of the more recent literature (Zandian et al. 2014) reported an overall success rate of 76% from a literature review of 4 papers, again reporting on small series of children with Dandy-Walker malformation and hydrocephalus treated with an endoscopic third ventriculostomy. The results that have been reported adding choroid plexus coagulation in this specific subset of patients do not significantly differ in terms of success rate from the exclusive performance of an endoscopic third ventriculostomy.

Warf et al. (2010) retrospectively reviewed the CURE Children's Hospital of Uganda clinical database between 2004 and 2010 identifying 45 patients with DWC confirmed by CT scanning (25 with DWM, 17 with DWV, and 3 with MCM) who were treated for hydrocephalus by ETV/CPC.

The median age at treatment was 5 months (88% of patients were younger than 12 months). An ETV/CPC was successful with no further operations in 74% at a mean follow-up of 24.2 months.

One of the conditions that seems to negatively influence the results of ETV in patients with Dandy-Walker syndrome is the presence of associated CNS malformations, such as agenesis of the corpus callosum which might preoperatively allow the escape of CSF into the convexity subarachnoid spaces. Contrast dynamic CT scans, MRI with flow studies and flow-sensitive phase-contrast cine MRI images might help to make the correct patient's selection (Cinalli et al. 2004b). Anatomic modifications of the interpeduncular cistern, the orientation of the third ventricular floor, the higher position of the tip of the basilar artery, and the displacement of the brainstem against the clivus are the conditions which usually make the endoscopic procedure difficult to perform. Endoneurosonography and transendoscopic Doppler ultrasound were proposed as technical adjuncts in order to identify intraoperatively parenchymal and vascular landmarks (Jodicke et al. 2003). Controlled CSF leak through the endoscope may allow a slow decompression of the cyst, which in turn may reduce the mass effect on the brainstem and recreate the space for a safe ETV (Cinalli et al. 2004b).

Constrictive Hydrocephalus

Results of ETV in Myelomeningocele Patients

Third ventriculostomy has been proposed in the management of hydrocephalus in children with MMC since mid-1990s, but its role remains controversial. Actually the most relevant series is still the one of Teo and Jones (1996) who reported on 69 patients with an overall success rate of 72%. At a mean follow-up of 28 months (min. 12 months; max 17 years), a significant worse outcome was found in patients aged less than 6 month (12.5% success rate) if compared with their older counterpart (80% success rate). The authors also described significant differences in success rates if ETV was performed as first line of treatment or secondary procedure (29% vs. 84% success rate). Though not reaching statistical significance, other factors that predicted a favorable result were the presence of a triventricular hydrocephalus, a diameter of the third ventricle > than 4 mm, the evidence of normal or slightly reduced subarachnoid spaces. On the other hand, the previous cerebrospinal fluid infection and/or of an intraventricular hemorrhage were negative predictive factors. Mori et al. (2003) also observed differences in the outcome in patients aged less than 1 year as compared with their older counterpart (25% vs. 90% success rate). Other papers in the literature, though based on single case reports or series with limited numbers of patients, have challenged the just mentioned results, in particular the role of age and the lower success rate of primary versus secondary ETV. Fritsch et al.

(Fritsch and Mehdorn 2003) reported a 50% success rate which was independent from children's age at surgery. Similar results were reported in the multicenter study of Portillo et al. (2004) who referred an overall success rate of 21% in a series of 19 myelomeningocele patients, a rate which was not related with age or time when ETV was performed. In a recent series, Tamburrini et al. (2004) were not able to find significant differences between infants (<6 months) undergoing primary ETV (overall success rate: 70%) and older patients who underwent third ventriculostomy as secondary procedure at the time of malfunction of a previously inserted CSF shunt device (overall success rate: 60%). Such discordant results might be influenced by selection modalities of patients who are candidates to ETV. In the series of Tamburrini et al., only infants with pure triventricular hydrocephalus and normal sized fourth ventricle were included. Also MR showed normal sized or reduced subarachnoid spaces, and clinically no history of associated hemorrhage or infection should have been demonstrated. More recently the development of the ETV success score as a validation method for ETV has re-unlighted the perplexities about the indications to perform ETV in infants with MMC and hydrocephalus. According to this score, infants below 6 months of age have a 30% possibility of success of the procedure. This result has been validated again in an unselected series of 16 infants presented by Ogiwara et al. (2010), actually reporting an overall success rate of 31%. Since the first publication by Warf and Campbell in 2008 (Warf and Campbell 2008), an increasing interest has been devoted to the addition of choroid plexus coagulation to ETV. A success rate of 71% and 76% was reported in two consecutive papers by these authors (Warf and Campbell 2008; Warf 2011). Scarred cisterns and choroid plexus were the two main factors contributing to the failure of the procedure. A strict selection of the infants undergoing ETV was also suggested, more than 80% of the infants in Warf series harboring a radiologically evident aqueductal stenosis. These data were confirmed from the retrospective Hydrocephalus Clinical Research Network study who also pointed out that a significant differential factor for the success of the procedure was represented by the percentage of choroid plexus coagulation and ranged from 36% if the choroid plexus coagulation was less than 90% up to 82% when the choroid plexus coagulation was more than 90% (Kulkarni et al. 2016b). Results were also reproduced with similar success rates in a North American series, in which the overall success rate was 65%, but significantly differed if there was or not a previously implanted shunt or if the patient had a scarring of the cisterns. Without these two risk factors, the success rate of the procedure was 91% (Stone and Warf 2014).

With a wider approach, Beuriat et al. compared the long-term results of ETV plus CPC, which was performed in 32 children with ETV to which VPS was added (20 cases) and VPS alone (18 cases). The overall success rate of ETV plus CPC was not different from the contemporarily implant of a shunt after ETV (72% vs. 65%), suggesting a protective value specifically of ETV on the long-term implanted shunt survival (Beuriat et al. 2016). Pindrick et al. postoperatively evaluated the MR features of children who underwent a successful ETV plus CPC. Radiographic CSF turbulence appeared more frequently following ETV/CPC failure than after ETV/CPC success (55% vs. 18%, respectively; $p = 0.02$). The sensitivity and

specificity of CSF turbulence as a radiographic marker for ETV/CPC failure were 80% and 58%, respectively. The radiographic depiction of CP disappearance following ETV/CPC from pre- to postoperative imaging occurred in 20 of 30 patients (67%). Among the patients who responded unsuccessfully to ETV/CPC and ultimately required secondary shunt insertion, 71% (10 of 14 patients) demonstrated CP persistence on postoperative imaging. In contrast, 6% (1 of 18) of patients who were treated successfully by ETV/CPC demonstrated the presence of CP on follow-up imaging (Pindrik et al. 2016).

A further factor that has been suggested to possibly influence the success of the ETV in children with MMC is represented by the difficult anatomy, both to access the third ventricular floor and the cisternal space. A small Monro foramen and/or unrecognizable mammillary bodies and septation and abnormal veins have been, respectively, found in 50% and 60% of the cases, possibly rendering the procedure more difficult than in other type of patients, negatively influencing the final outcome (Pavez et al. 2006). Etus et al. recently confirmed these findings in a large multicenter series of spina bifida children. Variations and abnormalities of the third ventricular floor were documented in 41.1% of 455 children with myelomeningocele associated hydrocephalus (Etus et al. 2016).

The most common anatomical features in this context were –“thick and prominent massa intermedia” – (37.1%) and – “narrow tuber cinereum” – (33.1%). Concerning subarachnoid spaces under the third ventricle floor, we should not forget the typical feature of the interpeduncular cistern in spina bifida children, commonly appearing as spiderweb shaped with a deep dislocation of the diencephalic duplication of the Liliequist membrane (Etus et al. 2016). In the era of fetal repair of MMC, discussion has also started on if patients with a persistent hydrocephalus after in utero surgery might show a better outcome if the hydrocephalus was treated with an ETV. In the series of Elbabaa et al., of a total of 30/55 children with persisting hydrocephalus after fetal repair of the MMC 25 underwent ETV, with an overall success rate of 45.1%. ETV age ≤ 6 months and gestational age ≥ 23 weeks at repair of myelomeningocele were significant predictors for ETV failure, while in-utero ventricular stability ≤ 4 mm and in-utero ventricular size postrepair ≤ 15.5 mm were significant predictors for ETV success (Elbabaa et al. 2017).

The slow and insidious progression which characterizes the evolution of this specific form of hydrocephalus in a large portion of subjects is an issue that has been discussed as possibly leading to wrong claiming of a success after the surgical operation in patients who actually continue to have a chronic hydrocephalus. As a consequence, strict neuroradiological, ophthalmological, and neuropsychological follow-up control is mandatory.

How to Evaluate the Outcome of ETV

Despite the accuracy of patients selection, several reports show that in a significant number of cases the symptoms and signs of increasing intracranial pressure related to hydrocephalus are however not controlled by the procedure (Hirsch et al. 1984;

Cinalli et al. 1999). The phenomenon is more frequently observed in the immediate postoperative period (early failures), being only sporadically observed in a later phase, usually within 5–6 years from the operation (late failures). Recurrence of hydrocephalus beyond this period has been reported exceptionally (Beems and Grotenhuis 2004; Cinalli et al. 1999; Tuli et al. 1999). The evaluation of the results immediately following the procedure may be sometimes difficult. After the opening of the third ventriculostomy, the increased amount of circulating CSF may require a so-called “adaptation period” (Hopf et al. 1999b; Bellotti et al. 2001; Cinalli 2004) to circulate or to be re-absorbed. This could explain the persistence of symptoms and increasing ventriculomegaly at MR scans examination that can be erroneously interpreted as failure of the procedure and indication to perform a VP shunt.

Among symptoms and signs, intracranial hypertension tends to resolve early following a successful procedure in the great majority of the operated on patients. In particular, Parinaud’s sign, if present preoperatively, is expected to disappear from the earliest postoperative moment; persistence of this sign should be taken as a potential predictor of failure (Cinalli 2004). Papilledema disappears within 2–3 weeks. Feng et al. (2004) found that an early satisfactory clinical response (within 2 weeks after the surgical operation) provided a high correlation with the overall ETV success.

Persistently high clinical ICP symptoms are particularly difficult to be detected in infants. In these patients, the most frequent sign of increased ICP, in spite of an apparent good clinical condition are swelling at the level of the coronal incision due to subcutaneous accumulation of CSF or, in some cases, CSF leaks. The situation is different when ETV is performed on patients operated on for shunt malfunction or presenting with slit ventricles. These patients may have significantly lowered intracranial compliance due to cephalocranial disproportion induced by the shunt and may exhibit a progressive clinical deterioration as their ICP may tend to increase in the first 7–10 days after surgery. Consequently, ICP monitoring and safety external ventricular catheter (EVC) to be placed into the same corticotomy track produced by the endoscope should be considered as mandatory in this context.

From a neuroradiological point of view, the volume decrease is much slower and smaller in scale after third ventriculostomy if compared with extrathecal shunts. Apart from the “adaptation period” (Hopf et al. 1999b; Bellotti et al. 2001), the persistence of the ventricular dilation in the early postoperative phase might be related to the lack of communication with a lower pressure cavity (e.g., right atrium, peritoneal cavity), and the chronic evolution of the ventricular dilation in case, for example, of hydrocephalus related to aqueductal stenosis, which often evolves over several years before becoming symptomatic (Fukuhara et al. 2000).

Basic MR acquisitions parameters that are expected to change after ETV are represented by global reduction of ventricular size with a variation between 10% and 50%, with disappearance of periventricular edema (when present) (Cinalli 2004; Schwartz et al. 1999), change of the position of the third ventricle floor to straight if preoperatively bulging downward, and disappearance of any atrial diverticula and pseudocystic dilation of the third ventricle.

In the context of ventricular volume change, the width of the third ventricle is the quickest to decrease and its reduction $\geq 15\%$ at 1 month is the most reliable indicator of a favorable outcome (Schwartz et al. 1996; 1999; Buxton et al. 2002; Tisell et al. 2000).

A decrease in volume of less than 10% may be observed in patients with long-standing chronic symptoms (Schwartz et al. 1999).

Cine-phase contrast MRI sequences, or alternatively sagittal T2 turbo SE sequences, are aimed to show directly the patency of the stoma and are still actually considered as a reference in the evaluation of the success of an ETV with a reliability of 75–80% (Feng et al. 2004). These sequences are even more relevant if used in the follow-up of children treated for their hydrocephalus through an ETV. They should be acquired in the first postoperative week before discharge in order to have a baseline exam when the stoma is certainly patent; subsequently they are performed at different time distances depending from age of the child, cause of the hydrocephalus, and wideness of the flow-void signal. From a recent review of the literature, Lam et al. found that when ETV is performed in infants and toddlers, the critical time for ETV closure is represented by the first 2 years; 75% of ETV closures occur during the first year after surgery in infants below 6 months of age, a further 25% occurring between the first and the second year after surgery. Almost all ETV closures occur by one year in infants operated on between 6 months and 1 year of age. A wider distribution of ETV closures is evident in older children; though still the majority of ETV failures occur in the first 2 years after surgery, 10–20% of ETV closures occurs by the third and fourth year (Lam et al. 2014). Concerning etiology ETV failure occurs in the first 3 months after surgery in almost all children with postinfective, spina bifida related, and posthemorrhagic hydrocephalus. ETV failures in children with congenital and tumoral hydrocephalus tend to be more sparsely distributed along the first 3–5 years after the procedure. On these grounds all children below 1 year and/or with any risk factor (i.e., posthemorrhagic, postinfective, or spina bifida-related hydrocephalus etiology) should be strictly monitored through AF ultrasounds (if AF is open) done monthly, and in case no clinical or ultrasound sign of ETV failure is present, they should undergo a control MR at 6 months from surgery and then at 1 year. On the other side children above one year of age with no added etiology related risk factor can be followed clinically at 1, 3, 6, 9 months and perform a control MR at 1 year from surgery. A flow-void reduction during the follow-up should be considered as a further risk factor inducing to anticipate MR controls when detected. Another point of discussion is how long we should follow children who underwent an ETV procedure.

Complications

There is a certain variation regarding reported complication rates of ETV among different centers. Such a variability depends from the lack of universally accepted criteria on what should be considered a complication, but also to true differences among centers, according to the individual surgeon and center experience in

performing the procedure. Hence, reported rates vary from 0% in series reporting only major complications to 31.2% in series reporting all minor incidents related to the operation. Most series, however, report rates between 5% and 15%, and in a meta-analysis performed by Bouros and Sgouros, the overall complication rate has been reported to be 8.5% (Bouros and Sgouros 2013).

Intraoperative Complications

The most frequent intraoperative complication is represented by hemorrhage, which may take place during various steps of ETV. Bleeding may occur immediately after the entrance of the endoscope in the lateral ventricle, due to the rupture of small cortical, parenchymal, or ependymal vessels or may occur during the passage of the endoscope in the third ventricle through the foramen of Monro. In this case the hemorrhage may be more severe, but most importantly, it might be associated to the injury of important veins, such as the thalamostriate vein, whose accidental closure leads to a venous infarct in the basal ganglia. Bleeding of minor vessels during the opening of the stoma on the floor of the third ventricle is common. This kind of hemorrhage usually stops with irrigation and local compression of the stoma border with the Fogarty balloon. The most scaring intraoperative complication of ETV is represented by the rupture of the basilar artery, which may occur in this step of the operation. The vessels at greatest risk are, in fact, represented by perforating arteries originating from the basilar trunk, which have a very thin wall, and even in the absence of a dolichoectatic basilar trunk might have a variable and irregular course from their origin up to the level of the brainstem. To avoid this complication, the surgeon must choose carefully the location of the ventriculostomy. 3D MR sequences might be helpful in this context, allowing to have a high definition of the anatomical structures under the third ventricle floor. In young patients with very large ventricles, the basilar artery is generally also visible through the thinned floor of the third ventricle. However, in older patients or if there have been previous episodes of ventricular hemorrhage or CSF infection, the floor may be thickened and the position of the basilar artery difficult to identify. If rupture of the basilar artery or perforating vessels occurs, performance of the cisternostomy should be abandoned; the endoscope should be left in place to deliver irrigation at the site of the vascular injury, a strategy which usually leads to stop the hemorrhage in 10–15 min. After the stop of the hemorrhage an external ventricular drain should be left in place until the CSF clears. The intraoperative bleeding rate varies from 0% to 8.5%, considerable hemorrhagic incidents having been described in 1–4% of the cases; of these, basilar artery or perforating vessels rupture has been reported in 0.2% of the cases. Intraoperative injury of neural structures has been only occasionally reported. However, this kind of complication is most probably understated, seen the reported rates of neurological morbidity. The most commonly reported injury is oculomotor nerve damage, which might occur at its entrance to the cistern; damage to the fornix while passing the Monro foramen, the thalamus, and the midbrain have also been reported with an incidence each of 0.1%. Damage of the hypothalamus might occur

in case of a too anterior stoma but generally is revealed after surgery by the evidence of hormonal deficiencies. Finally, from the anesthetic point of view, episodes of bradycardia and hypotension have been not infrequently reported. They are benign and resolve spontaneously or after atropin administration; the need to abandon the procedure as a consequence of one of these episodes has been described in 0.2% of the cases (Bouros and Sgouros 2013).

Immediate Postoperative Complications

The most frequent postoperative complication of ETV is CSF leak from the skin incision which has been reported in 0% to 5.2% of the cases with a mean rate of 1.7% (Bouros and Sgouros 2013). It is often the sign of an early ETV failure, though it can occur even in cases of successful ETV due to a persisting increase of the intraventricular pressure or in a minority of the cases is due simply to a poor wound closure. According to the cause of the CSF leak, treatment consists on the resolution of the persisting increase of the intraventricular pressure and or ETV failure (redo-ETV or extrathecal shunt implant), CSF subtraction through a safety implanted ventricular catheter or serial lumbar punctures, or, in case of selective wound dehiscence, resuturing of the skin wound. Infectious complications have been reported with a rate varying between 0% and 6.1%, most commonly related to CSF leak. Though exceptionally reported in detail, all types of intracranial hematomas may occur after an ETV; overall considered postoperative intracranial hemorrhage occur with a rate of approximately 1%. Apart from those hemorrhages occurring as a consequence of an intraoperative incident, which are most frequently intraventricular, epidural and subdural hematomas are mainly the consequence of an abrupt and not controlled lowering of the intracranial pressure (e.g., at the time of the subtraction of the endoscope). Subdural hygromas are on the other side most commonly the consequence of an impaired CSF resorption, most typically occurring in infants (Bouros and Sgouros 2013).

Neurological and Endocrinological Morbidity

Transient postoperative neurologic deficits have been extensively described, though with a variable rate, and include both focal neurological deficits and/or an impairment of consciousness, memory, and seizures. These last occur most frequently in the immediate postoperative period, and there has been a relation with the use during the procedure of saline solution for washing and rinsing the ventricles. Permanent neurological deficits occur in 1.2% of the patients. Focal motor deficits are the consequence of direct damage of the thalamostriate structures or damage of the thalamostriate veins, actually presenting in 0.4% of the cases. Even rarer are permanent gaze palsy (due to trauma of the oculomotor nerve, if the stoma is off the midline of the floor of the third ventricle), memory disorders (as a result of forniceal injury), and consciousness disorders. The most common hormonal disorder

described after ETV is diabetes insipidus, due to hypothalamic injury, transient in the great majority of the cases, persisting only in 0.5% of the patients. Weight gain, precocious puberty, and growth retardation are the other occasionally described hormonal disorders (Bouros and Sgouros 2013).

Mortality

At present the overall ETV procedure-related mortality rate that can be considered as worldwide accepted is 0.3%. The most frequent causes of immediate postoperative death are major hemorrhagic events due to intraoperative basilar artery or perforating vessels rupture or severe neurological deficits related to a direct or indirect damage to the brainstem.

Though still to be considered as sporadic, an increasing number of cases of late sudden death of children who have previously undergone otherwise uneventful ETVs are reported. Up to now we do not have a valid estimation of the possibility of occurrence of late death in children who have undergone an ETV. The two most important studies report 16 cases in total, collected from various centers worldwide; according to them, a rapid and often lethal deterioration could occur from 5 weeks to 7.8 years after ETV, and the finding is almost always stoma occlusion (Bouros and Sgouros 2013). The meta-analysis performed recently by Bouros and Sgouros calculated that this kind of lethal complication might occur with a rate of 0.07%, a rate which is most probably an underestimation of the true possibility of late sudden death occurrence. For this reason, all parents should be carefully informed of this possibility, and a strictly ruled follow-up should be performed in order to try to prevent this occurrence (Bouros and Sgouros 2013).

Conclusion

Endoscopic treatment of hydrocephalus is actually the mainstay of treatment for pure obstructive forms of hydrocephalus; the developing of new technology and gain of experience have led initially to extend the use of neuroendoscopic techniques to a variety of hydrocephalus etiologies in the first 20 years of modern ventricular endoscopy. The continuous development of new MR sequences (i.e., cine cardiac phase contrast and 3D CISS) have then added value to the definition of correct indications as well as in the way to follow-up treated patients. A further significant improvement has come from new vision and direction tools, such as 4K screens, videoscopes, and the wide use of magnetic neuronavigation. With prospective trials and scales, we are now able to foresee with more precision the results in single patients, something that has led the pediatric neurosurgical community to restrict the indications with a more reliable selection process. Technical pitfalls have become clearer, and awareness has been raised on how to avoid complications. The present era of endoscopic third ventriculostomy in the management of pediatric hydrocephalus has therefore entered the way of precision medicine; its continuous development

at all stages is destined to render this process a long fascinating address not only to the treatment but also to the understanding of the still many unknown mechanisms at the base of the pathophysiology of CSF dynamic disorders.

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