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Preface

Advances and Technical Standards in Neurosurgery was conceived in 1972 by its founding fathers Jean Brihaye, Bernard Pertuiset, Fritz Loew and Hugo Krayenbühl at a combined meeting of the Italian and German Neurosurgical Societies in Taormina. It was designed to complement the European post-graduate training system for young neurosurgeons and was first published in 1974 initially through sponsorship by the European Association of Neurosurgical Societies. All contributions have been published in English to facilitate international understanding.

The ambition of all successive editorial boards has been to provide an opportunity for mature scholarship and reflection, not constrained by artificial limits on space. The series provides a remarkable account of progress over the past 35 years, both with regard to advances, detailed descriptions of standard operative procedures and in- depth reviews of established knowledge. The present volume is no exception and should appeal to both experienced neurosurgeons and young neurosurgeons in training alike.

The Editors

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Standards

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Advances

Present and potential future adjuvant issues in high-grade astrocytic glioma treatment

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Abstract

Despite major advances in the management of malignant gliomas of which glioblastomas represent the ultimate grade of malignancy, they remain characterized by dismal prognoses. Glioblastoma patients have a median survival expectancy of only 14 months on the current standard treatment of surgical resection to the extent feasible, followed by adjuvant radiotherapy plus temozolomide, given concomitantly with and after radiotherapy.

Malignant gliomas are associated with such dismal prognoses because glioma cells can actively migrate through the narrow extra-cellular spaces in the brain, often travelling relatively long distances, making them elusive targets for effective surgical management.

Clinical and experimental data have demonstrated that invasive malignant glioma cells show a decrease in their proliferation rates and a relative resistance to apoptosis (type I programmed cell death) as compared to the highly cellular centre of the tumor, and this may contribute to their resistance to conventional pro-apoptotic chemotherapy and radiotherapy. Resistance to apoptosis results from changes at the genomic, transcriptional and post-transcriptional level of proteins, protein kinases and their transcriptional factor effectors. The PTEN/PI3K/Akt/mTOR/NF-κB and the Ras/Raf/MEK/ERK signaling cascades play critical roles in the regulation of gene expression and prevention of apoptosis. Components of these pathways are mutated or aberrantly expressed in human cancer, notably glioblastomas. Monoclonal antibodies and low molecular-weight kinase inhibitors of these pathways are the most common classes of agents in targeted cancer treatment. However, most clinical trials of these agents as monotherapies have failed to demonstrate survival benefit.

Despite resistance to apoptosis being closely linked to tumorigenesis, tumor cells can still be induced to die by non-apoptotic mechanisms such as necrosis, senescence, autophagy (type II programmed cell death) and mitotic catastrophe. Temozolomide brings significant therapeutic benefits in glioblastoma treatment. Part of temozolomide cytotoxic activity is exerted through pro-autophagic processes and also through the induction of late apoptosis. Autophagy, type II programmed cell death, represents an alternative mechanism to overcome, at least partly, the dramatic resistance of many cancers to pro-apoptotic-related therapies.

Another way to potentially overcome apoptosis resistance is to decrease the migration of malignant glioma cells in the brain, which then should restore a level of sensitivity to pro-apoptotic drugs.

Recent series of studies have supported the concept that malignant gliomas might be seen as an orchestration of cross-talks between cancer cells, microenvironment, vasculature and cancer stem cells.

The present chapter focuses on (i) the major signaling pathways making glioblastomas resistant to apoptosis, (ii) the signaling pathways distinctly activated by pro-autophagic drugs as compared to pro-apoptotic ones, (iii) autophagic cell death as an alternative to combat malignant gliomas, (iv) the major scientific data already obtained by researchers to prove that temozolomide is actually a pro-autophagic and pro-apoptotic drug, (v) the molecular and cellular therapies and local drug delivery which could be used to complement conventional treatments, and a review of some of the currently ongoing clinical trials, (vi) the fact that reducing the levels of malignant glioma cell motility can restore pro-apoptotic drug sensitivity, (vii) the observation that inhibiting the sodium pump activity reduces both glioma cell proliferation and migration, (viii) the brain tumor stem cells as a target to complement conventional treatment.

Keywords: High-grade gliomas; apoptosis resistance; chemotherapy; temozolomide; tyrosine kinase inhibitors; cellular and molecular therapies; clinical trials.

Introduction

Malignant gliomas continue to remain incurable, and the aim of multidisciplinary treatment is to improve neurological deficits and to increase survival while maintaining the best possible quality of life [30, 67]. The standard treatment for high grade gliomas is surgery followed by radiotherapy and chemotherapy. Maximum surgical resection constitutes the mainstay of treatment for operable high-grade gliomas [40, 60]. The extent of tumor removal and the residual tumor volume correlate significantly with median tumor progression and survival time [40, 60]. In a study involving 416 patients with glioblastoma multiforme a significant survival advantage was associated with the resection of 98% or more of the tumor volume [57]. A recent analysis carried out by Chang and colleagues [13] on 565 patients with newly diagnosed high grade gliomas showed that tumor resection was attempted on most of the patients (75%), with most (87%) receiving radiotherapy, and only 54% chemotherapy. It seems that practice patterns varied significantly between academic and community settings [86]. Establishing further clinical guidelines together with a best knowledge of the ongoing clinical trials may help reduce variability in practice patterns and increase the number of patients included into promising trials. O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, age, performance status, extent of resection, and Mini-Mental State Examination (MMSE) are suggested as eligibility or stratification factors for future trials in patients with newly diagnosed

glioblastoma [31]. Moreover, stratifying by MGMT promoter methylation status should be mandatory in all glioblastoma trials that use alkylating chemotherapy [31].

Despite the advances in the management of malignant gliomas, their prognosis remains poor. After the surgical resection and the adjuvant treatment of a glioma, the residual tumor cells peripheral to the highly cellular removed part of the lesion give rise to a recurrent tumor which, in more than 90% of the cases, develops immediately adjacent to the resection margin or within 2 cm of the resection cavity [61]. At recurrence, reoperation should be considered associated with a morbidity/mortality rate similar to at following initial surgery. It is evident that progressive neurological dysfunction may develop despite the absence of a mass effect or a recurrent bulk disease. This indicates that the infiltrative disease significantly contributes to the unsatisfactory course of events for glioma patients.

Natural resistance of migrating malignant glioma cells to apoptosis (radiotherapy and chemotherapy)

Clinical and experimental data demonstrate that invasive glioma cells show a decrease in their proliferation rates and a relative resistance to apoptosis as compared to the highly cellular center of the colony, and this may contribute to their resistance to conventional pro-apoptotic chemotherapy and radiotherapy [28, 61].

The natural resistance of glioblastomas to radiotherapy and chemotherapy is attributed, at least partly, to the PTEN (phosphatase and tensin homologue on chromosome ten)/Akt/PI3K (phosphatidylinositol 3-kinase)/mTOR (*the mammalian target of rapamycin*)/NF-κB pathway [54–56, 61, 64, 95, 100, 132] (Fig. 1). The activity of the PI3K/Akt pathway is often up-regulated in brain tumors due to excessive stimulation by growth factor receptors and Ras [85, 88]. PTEN tumor suppressor gene mutations which result in activation of the PI3K-dependent activation of Akt signaling [52, 88] are frequent in *de novo* glioblastomas [52]. Methylation of the PTEN promoter may represent an alternate mechanism by which PI3K signaling is increased in grade II and III gliomas as well as secondary glioblastomas [132]. The activation of the PI3K pathway is associated significantly with increasing tumor grade, lower levels of apoptosis and an adverse clinical outcome in the case of human gliomas [11]. Narita *et al.* [83] and Choe *et al.* [15] suggest that the PI3K/Akt pathway is a particularly interesting target in the case of glioblastomas with aberrant EGFR (*epidermal growth factor receptor*) expression, because the aberrant EGFR expression and abnormal PI3K/Akt signaling also modulate the levels of migration of tumor astrocytes [61]. A number of publications have already reported that an aberrantly activated PI3K/Akt pathway renders tumor cells

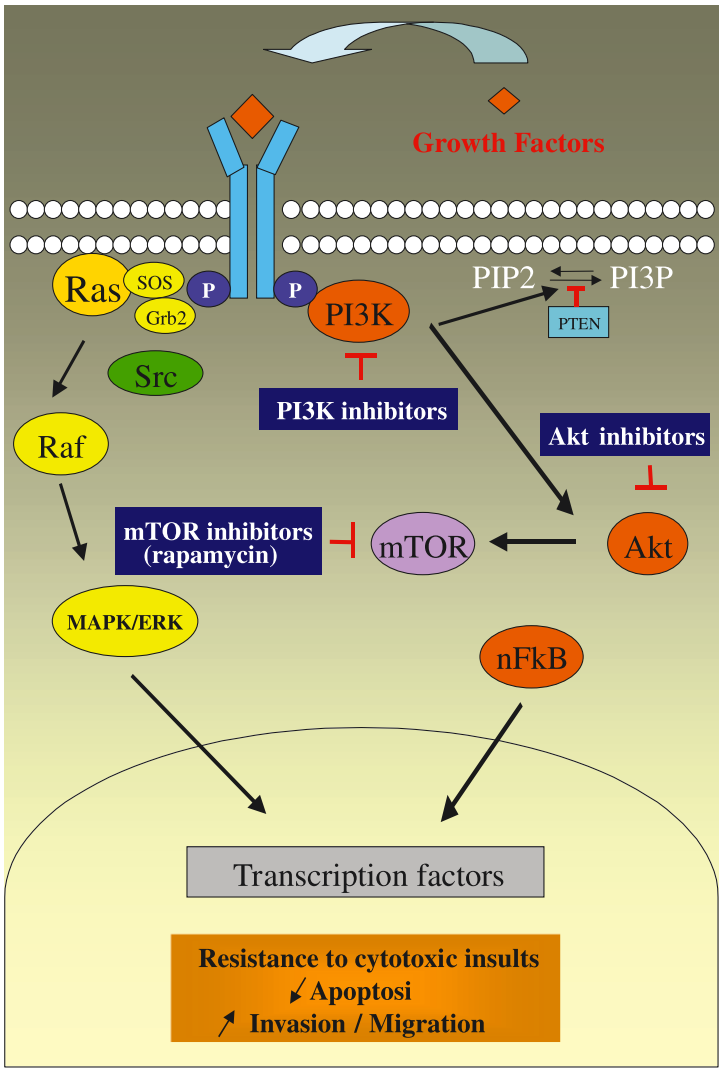

Fig. 1. Pathways involved in the natural resistance of glioblastomas to apoptosis (radio/chemotherapy). Pathways involved in cytotoxic insult resistance are presented in orange and the inhibitors that could be used to restore chemosensitivity to pro-apoptotic drugs are presented in blue. The binding of a ligand to EGFR causes receptor dimerization leading to tyrosine kinase activation. The resultant receptor autophosphorylation initiates signal-transduction cascades involved in cell proliferation and survival. Antibodies block the binding of ligands to the receptor, thereby inhibiting receptor phosphorylation and events downstream. Drugs have also been developed that inhibit the activity of the intracellular tyrosine kinase domain and so inhibit receptor autophosphorylation. Other drugs specifically block proteins of the downstream signal transduction involved in cell proliferation, migration and survival. Phosphatase and tensin homologue (PTEN) gene mutation or methylation promotes Akt activation

resistant to cytotoxic insults, notably to anti-cancer drugs [47, 114, 115]. Shingu *et al.* have shown that the inhibition of this pathway restores or even augments the effectiveness of chemotherapy on glioma cells [114, 115]. PI3K inhibitors could also be used to reduce the levels of tumor astrocyte migration, a feature that could restore a certain level of apoptosis to these cells [47]. Cell survival through Akt signaling also involves the NF-κB pathway because Akt signals to various cell-death regulators including IKK, which controls NF-κB activity. NF-κB itself plays a dramatic role in gliomagenesis [54, 61]. For example, the NF-κB signaling pathway is constitutively activated in a large proportion of glioblastomas [82] and this activation enables cancer cells to resist cytotoxic insults [1, 4]. The constitutive activation of Akt and NF-κB contributes significantly to the progression of diffuse gliomas, and the activation of Akt may lead to NF-κB activation in high-grade gliomas. As detailed below, cardenolide-induced inhibition of sodium pump activity leads to the deactivation of the NF-κB pathway.

Rapamycin inhibits the phosphorylation of the retinoblastoma protein (Rb), and rapamycin-treated glioblastoma cells are therefore not fully committed to entering the S-phase after their release from drug-induced G1 arrest [41, 112]. Constitutive Rb phosphorylation frequently occurs in glioblastomas due to mutation-induced p16 gene inactivation. mTOR can also control cell migration in glioblastomas [61].

Several strategies could be used potentially to overcome glioma cell resistance to cytotoxic insults: i) inhibition of the signaling pathways that are constitutively activated in a specific malignant glioma specimen, ii) use of inhibitors to reduce the levels of tumor astrocyte migration, a feature that could restore a certain level of apoptosis to these cells, iii) induction of autophagic cell death as opposed to apoptosis and iv) inhibition of sodium pump activity which disorganizes the actin cytoskeleton (reducing motility and proliferation) and induces autophagic processes in malignant glioma models. We further developed these new strategies in the treatment of high-grade gliomas.

Patterns of cell death

The therapeutic goal of cancer treatment has been to trigger tumor-selective cell death [126]. Although cell death can be achieved not only by apoptosis (type I programmed cell death) but also by necrosis, mitotic catastrophe and autophagy (type II programmed cell death), drugs inducing apoptosis remain the main chemotherapeutic agents in medical oncology [62, 90, 104].

Cell death can be divided into apoptotic cell death and non-apoptotic cell death [90]. The term apoptosis often has been used interchangeably with the term programmed cell death [90]. Apoptosis is the principal mechanism by which cells are physiologically eliminated. The original definition of apoptosis

Table 1. *Comparison of apoptosis, autophagy and necrosis*

	Apoptosis (Type I PCD)	Autophagy (Type II PCD)	Necrosis
Morphological changes			
Nucleus fragmentation	+	−	−
Chromatin condensation	+	−	−
Apoptotic bodies formation	+	−	−
Cytoplasmic vacuolation	−	+	+
Organelles degradation	−	+	+
Mitochondrial swelling	sometimes	late	+
Cytoplasmic swelling and Membrane breakdown	−	−	+
Biochemical features			
Caspase activity (caspase 3)	+	−	−
PARP	cleavage	−	activation
Lysosomal activity (cathepsin B)	−	+	−
Molecular pathways			
DAP	+	+	+
PI3-K, mTOR	−	+	
Bcl-2 proteins and cytochrome c	+	−	

DAP Death-Associated Proteins; *mTOR* mammalian target of rapamycin; *PARP* poly (ADP-ribose) polymerase; *PCD* Programmed Cell Death; *PI3-K* phosphatidylinositol 3-kinase.

as a form of cell death distinct from necrosis was based on morphological criteria (Table 1). Necrosis, traditionally been considered as an unregulated, passive, energy-independent form of cell death, has emerged as an alternate form of programmed cell death. Extensive failure of normal physiological pathways that are essential for maintaining cellular homeostasis, such as regulation of ion transport, energy production and pH balance can lead to necrosis. A classic example of necrotic conditions is ischemia that leads to a drastic depletion of oxygen, glucose, and other trophic factors and evokes massive necrotic death of endothelial cells and cells of surrounding tissues, such as in the center of large malignant tumors and which is the characteristic of glioblastomas. Because glioblastoma cells carry mutations that inactivate apoptotic pathways (Fig. 1) [61], necrosis could also represent an alternative pathway for tumor cells to be eliminated. Here after we describe autophagy, a mechanism for non-apoptotic programmed cell death that is distinct from apoptosis and necrosis by the criteria of morphology, biochemistry, and molecular pathways (Table 1) (Fig. 2) [64, 62].

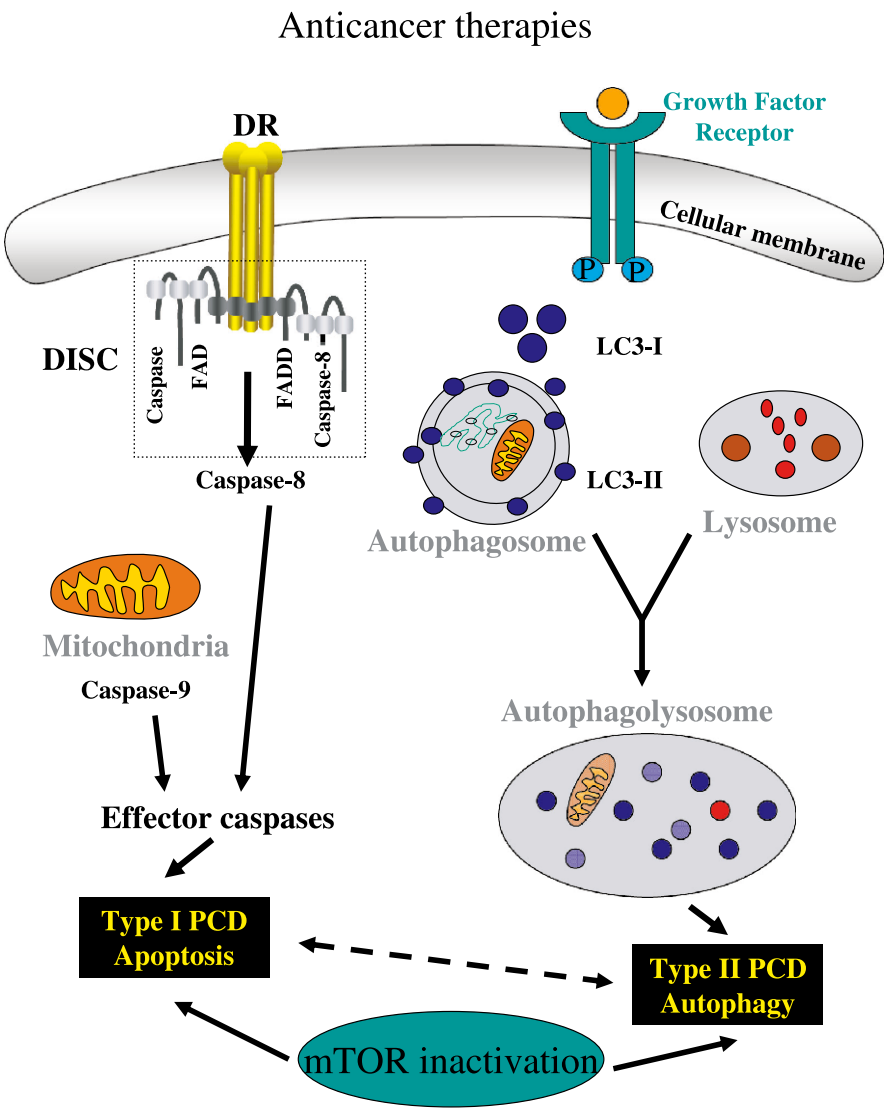

Fig. 2. The molecular regulation of autophagy and the link with apoptosis. In the presence of growth factors, growth factor receptor signaling activates cascades to the mammalian target of rapamycin (mTOR), resulting in the inhibition of autophagy or type II programmed cell death (PCD: right hand side of the figure). In contrast, inactivation of mTOR can induce both apoptosis and autophagy. The left hand side of the figure represents a simplified version of the two main signaling pathways of apoptosis. The intrinsic pathway includes the mitochondria. The extrinsic cell death pathway is mediated by death receptors (DR). After formation of the death receptor (DR)/DISC complex and recruitment of caspases, downstream signaling pathways lead to apoptosis

Autophagy: a potential Trojan horse for malignant gliomas

As recently reviewed by Okada and Mak [90] and ourselves [61, 62], resistance to apoptosis is closely linked to tumorigenesis, but tumor cells can still be induced to die by non-apoptotic mechanisms such as necrosis, senescence, autophagy and mitotic catastrophe. Autophagy is a novel concept in cancer research and malignant transformation is frequently associated with the suppression of autophagy [89].

As glioblastoma cells carry mutations that inactivate apoptotic pathways (Fig. 1) [61], non-apoptotic cell death could represent an alternative for apoptosis-resistant glioma cells to be destroyed [62, 64]. While apoptosis is a caspase-dependent process characterized by the condensation of cytoplasm and the preservation of organelles, essentially without any autophagic degradation, autophagic cell death is a caspase-independent process that exhibits extensive autophagic degradation of the Golgi apparatus, the polyribosomes and the endoplasmic reticulum (Table 1) (Fig. 2), with all these features preceding the destruction of the nucleus [53, 62]. Autophagy begins with the sequestration of cytoplasmic organelles into membrane vacuoles called autophagosomes which then fuse with lysosomes to form autolysosomes, in which materials are subsequently degraded and recycled (Figs. 2 and 3) [49, 53, 64].

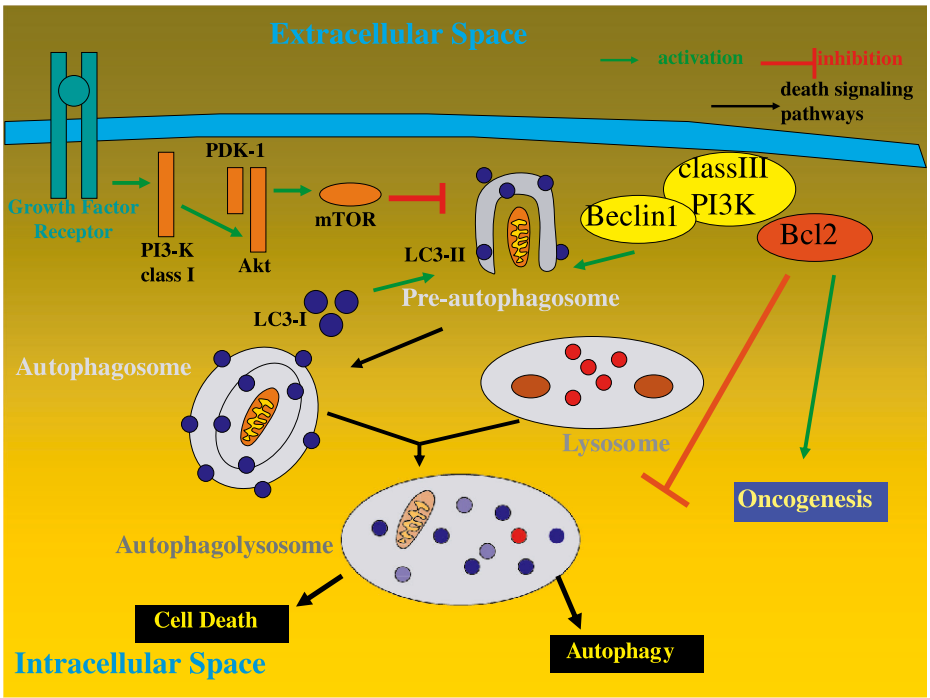

Fig. 3. Simplified view of the pathways of autophagy

The autophagic process in mammalian cells is regulated by homologues of the Apg and Aut autophagy-relevant family of yeast genes, now renamed Atg genes [103]. Several Atg proteins have been implicated in autophagosome formation (Fig. 3). Atg5, Atg7, Atg10 and Atg12 are required to form the autophagic vacuole (Fig. 3). PI3K, the enzyme synthesizing phosphatidylinositol-3-phosphate (PtdIns 3P) from PtdIns, is a major player in mammalian autophagic pathways. While class III PI3K is required in the early stages of autophagosome generation, class I PI3K activity has an inhibitory effect, mediated at least partially through mTOR (Fig. 3) [53, 64]. Thus class I PI3K, Akt and mTOR are components of the pathways that are involved both in apoptosis and autophagy resistance of cancer cells (Figs. 1 and 3). Beclin 1, a homologue of the yeast autophagy protein Atg6, which belongs to the class III PI3K complex, is required for vacuolar formation and transport (Fig. 3) [53]. In addition to interacting with class III PI3K, beclin 1 is able to bind Bcl-2 pro-apoptotic family members (Fig. 3) [94]. While beclin 1's interaction with class III PI3K stimulates autophagy and inhibits oncogenesis, its interaction with Bcl-2 inhibits autophagy and stimulates oncogenesis (Fig. 3) [94]. Autophagy is also induced by the cell death-associated protein kinase (DAPK) and the death-associated related protein kinase 1 (DRP1) [53, 64]. Recent research has also revealed that autophagy is activated by p53, the guardian of the genome, a critical tumor suppressor that is involved and mutated in more than 50% of cancers of all tissue origins [24, 44]. Crighton *et al.* have described a damage-regulated autophagy modulator gene (DRAM), a p53 target gene encoding a lysosomal protein that induces autophagy [17]. Like beclin 1, analysis of DRAM in a subset of epithelial tumors revealed frequent decreased expression [17]. Finally, MAP1LC3, the microtubule associated-protein 1 light chain 3, exists in two forms, MAP1LC3-I localized in the cytosol and its proteolytic derivative MAP1LC3-II localized in autophagosomal membranes (Fig. 3) [53]. During autophagy, MAP1LC3-I is cleaved and conjugated to phosphatidylethanolamine to form MAP1LC3-II which is essential for the formation of the autophagosome [53]. MAP1LC3-II thus can be used to estimate the abundance of autophagosomes before they are destroyed through fusion with lysosomes (Fig. 3) [53].

mTOR seems to be involved in autophagic cell death as its inactivation can induce autophagy (Figs. 2 and 3) [62]. mTOR is a downstream effector of the PI3K/Akt signaling pathway (Fig. 1) and it is also a central modulator of cell proliferation in malignant gliomas [41, 124]. In fact rapid tumor proliferation (that can result from low apoptotic levels) may contribute to the clinical resistance of glioblastomas to radiotherapy, and disruption of mTOR signaling by rapamycin appears to return a certain level of sensitivity to resistant glioblastoma cells (Fig. 1) [22]. Takeuchi *et al.* showed that rapamycin induced autophagy but not apoptosis in rapamycin-sensitive malignant glioma U87-MG and T98G cells by inhibiting the function of mTOR [124]. In contrast, in rapamycin-

resistant U373-MG cells, the inhibitory effect of rapamycin is minor [124]. A number of potential common targets in apoptosis and autophagy resistance pathways i.e. mTOR, PI3K and Akt have been identified (Figs. 1 and 3). Inhibitors of such targets might be able to increase the level of sensitivity of migrating apoptosis-resistant cancer cells to both pro-apoptotic and pro-autophagic drugs (Fig. 1). Thus, novel successes in the fight against devastating cancers including glioblastoma might be achieved by the combination of pro-autophagic drugs such as temozolomide with mTOR, PI3K or Akt inhibitors as adjuvant chemotherapies and as illustrated by several ongoing clinical trials.

Recent results show for the first time that brain tumor stem cells are susceptible to adenovirus-mediated cell death via autophagy *in vitro* and *in vivo* [45], a topic that we developed after.

As traditional clinical end points prove more difficult to apply in evaluation of molecularly targeted therapies, a great need exists to define and validate surrogate markers of effect and benefit [110]. mTOR expression could be evaluated and high tumor mTOR protein levels might indicate suitability for a pro-autophagic inhibitor strategy. Most trials using mTOR inhibitors do not measure mTOR levels. Instead the commonly studied biomarkers are usually downstream effectors such as the phosphorylation of ribosomal p70 S6 kinase which is considered to be a good indicator of the activated Akt/mTOR pathway as well as rapamycin sensitivity [87]. Analysis of DRAM expression, a damage-regulated autophagy modulator gene encoding a lysosomal protein that induces autophagy could potentially also be used as a surrogate marker before the administration of a pro-autophagic drug. In addition, the analysis of MAP1LC3-II that estimates the abundance of autophagosomes before they are destroyed could be used to follow the pro-autophagic effects of a new compound. Similar analyses could also be performed to determine the activation status of other potential biomarkers (PI3K, Akt, NF-κB) in tumor tissues. It seems that whether activation of the PI3K pathway confers sensitivity or resistance to therapy depends on the therapy used, as well as secondary gene events [130]. Thus although genome-wide and proteomic profiling of tumors may orient the therapeutic choice, understanding the genotype-response relationships in human tumors will be important for the effective use of compounds targeting the PI3K pathway in the clinic. Evaluation of these potential biomarkers in preclinical studies can be used to help select lead pro-autophagic compounds and better define patients who will benefit from this treatment.

Therapeutic benefits of temozlomide

A source of real hope in glioma chemotherapy is offered by temozolomide, a second-generation imidazotetrazine alkylating agent [33, 67, 122]. Temozolomide is a small lipophilic molecule which can be administered orally and which

crosses the blood–brain barrier effectively. Moreover, temozolomide is less toxic to the hematopoietic progenitor cells than conventional chemotherapeutic agents and does not require any hepatic metabolism for activation [49]. An international clinical trial [122] has shown that the addition of temozolomide to radiotherapy increases the survival of patients suffering from newly diagnosed glioblastomas. Indeed, addition of temozolomide to radiotherapy improves median survival in newly diagnosed glioblastoma patients from 12.1 to 14.6 months and it increases 2-year survival from 10.4% to 26.5% [122].

Part of temozolomide's cytotoxic activity is exerted through pro-autophagic processes, at least in glioblastoma cells, due to the formation of O^6-methylguanine in DNA which mispairs with thymine during the next cycle of DNA replication [48, 49]. Glioma cells thus respond to temozolomide by undergoing G2/M arrest but will ultimately die from autophagy [48, 49]. While apoptosis is labeled as type I caspase-dependent programmed cell death, the type II caspase-independent process describes autophagic cell death. Knowing that O6-alkylguanine-DNA alkyltransferase (AGT) is a DNA repair enzyme that limits the efficacy of temozolomide in glioblastoma cells [48] showed that inhibition of AGT by O6-benzylguanine can render previously resistant glioblastoma cells sensitive to temozolomide. Hegi *et al.* and Chinot *et al.* showed that patients who had glioblastomas that contained a methylated MGMT (O^6-methylguanine-DNA methyltransferase) promoter benefited from temozolomide, while those who did not were less responsive [14, 37]. However, results contradicting these findings are present in the literature and the clinical and genetic context framing MGMT methylation is poorly characterized. Recent observations suggest that MGMT methylation is part of the genetic signature of glioblastomas that develop from lower-grade gliomas [21].

Part of temozolomide's cytotoxic activity is however also due to the induction of late apoptosis. Indeed Roos *et al.* [106] showed that malignant glioma cells undergo apoptosis following treatment with the methylating agents N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) and temozolomide. O(6)MeG-triggered apoptosis in gliomas is a late response (occurring >120 h after treatment) that requires extensive cell proliferation. Overall, the data reported by Roos *et al.* [106] demonstrate that cell death induced by temozolomide in gliomas is due to apoptosis and that determinants of sensitivity of gliomas to temozolomide are MGMT, p53, proliferation rate and double-strand break repair. Given that the response to temozolomide is at least partly associated with MGMT promoter methylation status, MGMT methylation analysis by means of RT-PCR techniques could be used to predict tumor sensitivity to the drug [37, 31]. However, this surrogate marker of response is not really related directly to the pro-autophagic phenomenon.

The data reported by Kanzawa *et al.* [49] and Roos *et al.* [106] are not contradictory because autophagy and apoptosis may be triggered by common

upstream signals, and sometimes this results in combined autophagy and apoptosis [62, 72] (Fig. 2). In other instances, the cell switches between the two responses in a mutually exclusive manner [72]. On a molecular level, this means that the apoptotic and autophagic response machineries share common pathways that either link or polarize the cellular responses (Fig. 2) [72]. We will show below that inhibiting sodium pump activity in human apoptosis-resistant glioblastoma cells can induce marked processes of autophagy.

Recent data have also emerged showing that temozolomide could be considered as a potential radiosensitizer [12].

Local therapies for glioblastomas

Recurrence near the tumor resection site may be due to changes in the extracellular matrix coincident with scar tissue. Moreover, the extracellular matrix that supports a migratory phenotype retards the growth rate of the cell population. In this sense, control of the disease by local therapy applied to the resection cavity during surgery may reduce the rate of local failure and increase the time for local progression. These agents function inside the tumor cells with microscopic and submicroscopic precision. Molecular therapies such as neural stem cells, immunotherapies, biodegradable polymers and convection-enhanced drug delivery could complement existing surgical, radiological, and chemotherapeutic approaches to the treatment of gliomas. However, local chemotherapy protocols using degradable polymers applied to the resection cavity depend on the diffusion of the drugs delivered to the brain parenchyma, which presumably lies within millimeters of the site of implantation [131].

The only FDA-approved drug delivery system consists of carmustine (BCNU)-impregnated polymers in the form of wafers (Gliadel®) [131]. These wafers are implanted into the tumor cavity during surgery and slowly release the active drug. As compared to empty polymers, this treatment significantly improves the survival of patients with newly diagnosed glioblastomas with both groups receiving radiotherapy after surgery [131]. This result seems similar to the benefit derived from systemic adjuvant nitrosoureas [121]. However, so far no studies have compared a systemic chemotherapy strategy with this local delivery.

One promising surgical technique for the delivery of drugs directly into the brain parenchyma involves a convection-enhanced delivery system (CED) [38]. CED uses positive pressure infusion to generate a pressure gradient that optimises the distribution of macromolecules within the tumor and the surrounding tissue [108]. This system is notable in a small number of treatments of recurrent high-grade gliomas. A first system uses interleukin-(IL)13-PE38QQR, a recombinant toxin composed of the enzymatically-active portion of Pseudomonas Exotoxin A conjugated with human IL13 binding selectively to IL13 alpha2 receptors overexpressed by malignant gliomas [43]. This re-

combinant cytotoxin (0.5 μg/mL) administered via CED before standard radiochemotherapy seems to be well tolerated in adults with newly diagnosed malignant gliomas [127]. Another system consists of a toxin conjugated with the EGFR binding ligand transforming growth factor-alpha (TGF-α) [107]. The binding of the ligand to the receptor (overexpressed or constitutively activated in malignant gliomas, Fig. 1) permits the internalisation of the recombinant toxin, and this results in a selective and potent cytotoxicity at nanomolar concentrations. In this context, the TransMID study uses transferrin-CRM107, a conjugate of human transferrin and diphteria toxin [129]. These are currently undergoing Phase III study. Recent data reveal that target tissue anatomy and catheter position are critical parameters in optimizing drug delivery [108].

Ongoing clinical trials for glioblastomas

Using as a reference the internet site http://www.clinicaltrials.gov/ct/search;jsessionid=854243DC237D32C8BED356A7ADB0F791?term=glioblastoma – a service developed by the National Library of Medicine for the US National Institute of Health – we obtained information on about 392 clinical glioblastoma management trials currently under way (12th February 2008) for resistant progressive glioblastomas or newly diagnosed ones. These studies include 102 clinical trials using temozolomide and 83 studies of combined therapy based on the hypothesis that combining more than one chemotherapy drug with radiotherapy may kill more tumor cells. We describe here the compounds used in the so-called target therapy to inhibit growth factor receptors and tyrosine kinases. Many of these drugs were generally well tolerated in clinical trials; however, as single-agents, the results have been disappointing. As emphasized by Omuro and Delattre [91], the oncogenetic process in such tumors is driven by several signaling pathways that are differentially activated or silenced with both parallel and converging complex interactions. Therefore, it has been difficult to identify prevalent targets that act as key promoters of oncogenesis and that can be successfully addressed by novel agents. Several drugs have been tested, including epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (gefitinib and erlotinib), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), and vascular endothelial growth factor receptor (VEGFR), protein kinase C-beta, and other angiogenesis pathways inhibitors (vatalanib, bevacizumab, and enzastaurin). Most of the present clinical trials evaluate conventional drugs in combination with target therapy which may improve their clinical activity. Ongoing investigations evaluating temozolomide in combination with other systemic agents, and additional agents (e.g., motexafin gadolinium, mammalian target of rapamycin inhibitors, farnesyltransferase inhibitors) seem to show promising activity in combination with radiotherapy [12].

Growth factor receptor inhibitors

Growth factor receptors such as EGFR and PDGFR, whose abnormal functioning leads to the accelerated clinical progression of malignant gliomas, have already been specifically targeted (Fig. 1). Highly specific small molecule inhibitors of these tyrosine kinase receptors have been developed [96, 97, 101, 105]. Gefitinib (Iressa) and erlotinib (Tarceva) are orally active selective EGFR inhibitors which were clinical tested with respect to a number of tumors, including malignant gliomas [96, 97, 105]. The accelerated approval of gefitinib for non-small lung cancer has been revoked by the Food and Drug Administration due to the lack of efficacy in published randomised phase III studies. In the same manner, in the absence of objective responses, some limited antitumor activity was suggested for the treatment of glioblastomas with gefitinib [105]. Objective responses were seen in phase I and phase II trials with erlotinib associated or not to TMZ for recurrent glioblastoma [97]. However, only 10–20% of patients respond to EGFR kinase inhibitors. On the basis of the sequencing of genomic tumor DNA and immunhistochemistry analysis it seems that the coexpression of EGFRvIII (EGFR deletion mutant variant III) and PTEN by glioblastoma cells is strongly associated with responsiveness to EGFR kinase inhibitors [76]. Data also suggest that the downstream inhibition of the PI3K pathway, perhaps at the level of the mammalian serine/threonine protein kinase target of rapamycin (mTOR) (as detailed below), could be combined with EGFR kinase inhibitors to promote responsiveness in patients with PTEN-deficient tumors [32].

PI3K/Akt, mTOR and NF-κB inhibitors

The clinical struggle against malignant gliomas should also include inhibitors against signaling pathways controlled by PI3K/Akt, mTOR and NF-κB (Fig. 1). Indeed, reducing the signaling abilities of PI3K, Akt, mTOR and NF-κB would not only reduce the growth levels of malignant gliomas, but should also reduce the migration levels of individual glioma cells migrating into the brain parenchyma [7]. This reduction in the migratory abilities of individual migrating glioma cells should restore pro-apoptotic drug sensitivity in these individual migrating glioma cells that are naturally resistant to apoptosis (and so to current chemotherapies) due to the constitutive activation of one or another of the PI3K/Akt, the mTOR or the NF-κB signaling pathways [88]. The fact remains that all these pathways are not activated at the same time in any single glioma. It remains unclear how best to integrate recent discoveries regarding glioma molecular biology into clinical practice [59]. Particular inhibitor(s) should therefore only be chosen if the target(s) is (are) present in the tumor tissue, but this is only possible if individual patients are submitted to the molecular profiling of their tumors. The stratification of cases has not yet been carried out in the

majority of trials conducted by the National Brain Tumor Consortia funded by the National Cancer Institute, the NABTC and the NABTT (New Approaches to Brain Tumor Therapy). This aim should be at least partly satisfied in the near future by integrating into clinical practice the data provided by molecular profiling as in the search for 1p19q deletion to identify glioma patients who are to benefit from intensive adjuvant chemotherapy.

Rapamycin, a macrocyclic lactone, is a highly specific inhibitor of mTOR [7], and mTOR is a direct target of the PI3K/Akt signaling pathway in mitogen-stimulated cells (Fig. 1) [7, 74]. Bjornsti and Houghton recently reviewed the TOR pathway as a target for cancer therapy [7]. As emphasized by Sekulié *et al.* [112], rapamycin is a potent immunosuppressive drug and investigational agent, the major mechanism of action of which involves the inhibition of cell proliferation mediated by blocking cells moving from the G1 to the S phase of the cell cycle. In fact, rapamycin inhibits the phosphorylation of the retinoblastoma protein, and rapamycin-treated cells are therefore not fully committed to entering the S-phase after their release from drug-induced G1 arrest [112]. Constitutive Rb phosphorylation frequently occurs in glioblastomas due to mutation-induced p16 gene inactivation and, as expected, clinical trials with mTOR inhibitors (including, for example, CCI-779) were proceeding on patients with recurrent glioblastomas [26]. This phase II trial of temsirolimus (CCI-779) in 65 recurrent glioblastoma patients has shown radiographic improvement in 36% of them, and was associated with significantly longer median time to progression [26]. Based on preclinical evidence that phosphatase and tensin homolog deleted on Chromosome 10 (PTEN) loss sensitizes tumors to the inhibition of mammalian target of rapamycin (mTOR) [16] conducted a proof-of-concept Phase I neoadjuvant trial of rapamycin in patients with recurrent glioblastoma, whose tumors lacked expression of the tumor suppressor PTEN.

Matrix metalloproteinase (MMP) inhibitors (MMPI)

Specific anti-migratory compounds should be added to conventional radio- and/or chemotherapy. MMP are zinc-dependent endopeptidases that degrade some components of the extracellular matrix. A review of MMP and the development of MMPI can be found [39]. MMP degrade the basement membrane and the extracellular matrix, thus facilitating tumor growth, invasion, and spread. MMP expression is enhanced in most cancers, including gliomas. Of all the known MMPI in clinical development, marimastat, metastat, and prinomastat have been, or are being, tested in trials against gliomas [35, 39]. Combined with temozolomide the MMPI marimastat has given the best results to date in phase II trials, increasing the rate of 6-month progression-free survival in cases of recurrent glioblastomas and anaplastic gliomas [35]. A more recent study revealed that even though this regimen was more efficacious than a comparator

of historical controls in recurrent anaplastic gliomas, the regimen was roughly equivalent to single-agent temozolomide and was associated with additional toxicity. The sub-analysis suggests pharmacokinetic and drug–drug interactions which may positively impact responses to marimastat [34].

Angiogenesis targeting

Malignant gliomas are remarkably angiogenic, and vascular endothelial growth factor (VEGF) is the dominant pro-angiogenic factor. Few trials use drugs to try to inhibit the formation of new blood vessels in glioblastomas and this type of approach has recently been reviewed by [98, 58]. Results have been published on phase II trials with thalidomide – a putative inhibitor of angiogenesis – in the treatment of adults with previously irradiated, recurrent high-grade gliomas [80]. Using the rabbit corneal micropocket assay it has already been shown that thalidomide inhibits basic fibroblast-growth-factor-induced angiogenesis and decreases the proliferation of endothelial cells in cultures without any modification to the proliferation of glioma cell lines *in vitro*. However, if thalidomide is generally well tolerated, it may display antitumor activity in a minority of patients only [80]. The clinical activity of a combination of thalidomide and temozolomide is currently being explored in a phase I/II trial in the case ofpatients with newly diagnosed glioblatomas (http://www.clinicaltrials.gov/ct/search;jsessionid=854243DC237D32C8BED356A7ADB0F791?term=glioblastoma).

Strategies of inhibition of vascular endothelial growth factor (VEGF), which increases vascular permeability and stimulates endothelial proliferation and migration and commonly overexpressed in glioblastomas, have been developed. The most positive results with targeted therapy remain to date the high response rates with bevacizumab and irinotecan in a phase II trial for recurrent malignant gliomas [91, 118]. The monoclonal antibody bevacizumab targets VEGF, the paracrine stimulator of angiogenesis. An update on survival from the original phase II trial of bevacizumab and irinotecan in recurrent malignant gliomas was presented at the ASCO annual meeting 2008 [128]. The overall response rates for both grade III and IV were 59% (grade III 61%, grade IV 57%), the 6-month period free survival and overall survival for grade III were 59% and 79% and for grade IV 43% and 74% respectively. For the grade IV patients, the 2yr overall survival is 15% [128]. Therefore, the combination of bevacizumab and irinotecan provides a clinically meaningful treatment option for patients with recurrent malignant gliomas. However, combination of anti-angiogenic drugs with more potent chemotherapy will probably be necessary.

An array of additional clinical trials evaluating anti-angiogenic strategies are underway for both recurrent and newly diagnosed malignant glioma patients [101].

Cellular and vaccination therapies

The discovery of dendritic cells, the most potent antigen presenting cells to initiate specific immune responses and the possibility of producing them *ex vivo* have given rise to new protocols of active immunotherapy against gliomas [20, 46]. Phase I clinical trials [10, 51, 134, 136] have shown that vaccination using patients' peripheral blood dendritic cells pulsed with tumor lysates, cell fusions, RNA, and/or peptides can elicit antitumor immune responses against CNS neoplasms. Dendritic cell vaccination elicits T-cell-mediated antitumor activity and intratumoral CD4+ and CD8+ T-cell infiltration [10]. Although the currently available clinical data are too limited to arrive at any conclusions concerning its effectiveness, the advantages of dendritic cell-based immunotherapy and its documented safety and feasibility have stimulated further development and testing. The data suggest that coupled with the low transforming growth factor $\beta 2$ expression within the glioblastomas, the absence of bulky, actively progressing tumor may identify a subgroup of patients to target as potential responders in future clinical investigations of dendritic cell-based vaccines [70].

Gene therapy

Researchers have been exploring many candidate genes, developing improved viral and non-viral vectors, trying different methods to deliver genes, and combining gene therapies with other modalities such as immunotherapy. Although the antitumor effect of these gene therapies looked very promising on animal models, the effect on human patients has been disappointing. The recent review by Kanzawa *et al.* focuses on current therapeutic genes/vectors/delivery systems/targeting strategies in order to introduce updated trends and, hopefully, to indicate a prospective gene therapy for malignant gliomas [50].

Gene therapy has been disappointing, but major improvements in gene delivery technology could renew an interest in it. RNA interference (RNAi) has the potential to knock down oncogenes. However, the therapeutic potential of RNAi will not be realised until the rate-limiting delivery step has been dealt with [93].

Reducing malignant glioma cell motility in order to restore pro-apoptotic drug sensitivity

For motility, cells must acquire spatial asymmetry enabling them to turn intracellular generated forces into net cell body translocation [61]. One characteristic of this asymmetry is a polarized morphology i.e. a clear distinction between the front and rear of cells. An early event in this polarization is a change in filamentous F-actin distribution from azimuthal symmetry around the cell rim to a concentration in a particular region [61]. Additional molecular rearrange-

ments consist of the redistribution of chemosensory signaling receptors, integrins and other adhesion receptors, and the redistribution of integrin-cytoskeleton linkages [61]. Another important consequence of polarization is that the extension of active membrane processes, including both lamellipodia and filopodia, takes place primarily around the cell front, so that directional turning is generally accomplished gradually, with cell locomotion taking on the character of a persistent random walk.

Lamellipodia are broad flat sheet-like structures, whereas filopodia are thin cylindrical needle-like projections. These structures contain an abundance of actin and actin-associated proteins [61]. The extension of both the lamellipodia and the filopodia in response to migratory stimuli is almost universally found in conjunction with local actin polymerization [61]. Along with a bias towards membrane extensions at the cell front, attachments tend to form preferentially at the leading edge of lamellipodia and filopodia [61]. Rapid migration also requires efficient mechanisms to release adhesion at the rear [61]. While the actin cytoskeleton provides the driving force at the front, the microtubule network assumes a regulatory function in coordinating rear retraction [61].

As indicated above one potential way of overcoming apoptosis resistance is by decreasing the migration of migrating glioma cells, which results in a net increase in the level of sensitivity of these cells to pro-apoptotic drugs [61]. We have recently shown that when compared to temozolomide alone cimetidine – an anti-inflammatory agent whose action against migrating epithelial cancer cells has now been proved – when added to temozolomide is superior *in vivo* in extending the survival of nude mice with human glioblastoma cells orthotopically xenografted into their brains [63]. The benefit from cimetidine is partly due to an antiadhesive and therefore antimigratory effect on glioma cells [63]. We have consequently reviewed the various mechanisms of action potentially associated with the therapeutic effects of cimetidine in the case of experimental glioblastomas [68], and hope that our observations will encourage the clinical investigation of cimetidine with respect to the management of highly malignant gliomas.

We also showed that when compared to temozolomide alone, the therapeutic benefits obtained *in vivo* in experimental models of human orthotopic glioblastomas were significantly more pronounced when combining temozolomide and a siRNA directed against galectin-1 [69], which is a potent modulator of glioma cell migration [9]. Similar data were obtained when we combined temozolomide with the targeting of sigma1 receptors in glioblastoma cells [75].

The sodium pump constitutes a new target to combat malignant gliomas

The growth of a glioma requires the destruction of the normal brain parenchyma by the glioma cells [117]. This is achieved through the cellular release of

glutamate into the peritumoral space [71] in the absence of functional Na^+-dependent glutamate transporters in glioma cells, resulting in the consequent accumulation of excitoxic glutamate in the extra-cellular glia space [123]. Signaling through glutamate receptors is also involved in glioblastoma cell proliferation [3]. Glioma cells are "self-propelled" [117] and are able to adjust their shape and volume rapidly as they invade the brain parenchyma. Essential to this process is the activity of chloride channels, anion transport mechanisms [99] and aquaporins [36]. The sodium pump is another ion transporter which in addition to exchanging cations is also directly involved in the migration of cancer cells in general [6, 23, 78, 79] and of glioma cells in particular [66, 113]. Moreover, the activity of NaK can be modulated by glutamate and its receptors [81].

The sodium pump

In mammalian cells, active sodium transport and its derived functions (e.g., plasma membrane potential) are dictated by the activity of the sodium pump, whose regulation is essential for maintaining cell volume and composition, as well as other vital cell functions [116]. Because the plasma membrane is highly permeable to water, it is the concentration of ions across this membrane that is, in the short term, critical for maintaining an adequate cell volume. The plasma membrane sodium pump is important in this process because it provides the driving force for active sodium and potassium transport into and out of the cell, with water following isosmotically [116]. Increases in sodium permeability require concomitant increments in sodium pump-mediated outward sodium transport to prevent a disproportionate increase in the intracellular sodium concentration/osmotic pressure and, consequently, cell swelling (Fig. 4A).

The sodium pump consists of equimolar ratios of two main subunits, the catalytic α and regulatory β polypeptides, each of which exists as several isoforms [79]. To date, four different α and three distinct β isoforms have been identified in mammalian cells [8, 79, 133]. The α subunit contains the binding sites for the above cations, ATP and cardiotonic steroid inhibitors [8, 79, 133]. While the β subunit is essential for the normal activity of the enzyme, it also appears to be involved in the occlusion of K^+ and modulation of the enzyme's K^+ and Na^+ affinity [79, 133]. In addition to pumping ions (Na^+ and K^+) across the plasma membrane (Fig. 4A), the sodium pump functions as a receptor for cardiotonic steroids [8, 79, 133] including ouabain, digitoxin and digoxin and a novel cardenolide UNBS1450 [66, 78, 79] (Fig. 4).

During apoptosis, there is compelling evidence indicating an early increase in intracellular sodium followed by a decrease in both intracellular K^+ and Na^+ suggesting a regulatory role for these cations during both the initial signaling, and the execution phase of apoptosis [133]. Recent studies have shown that the

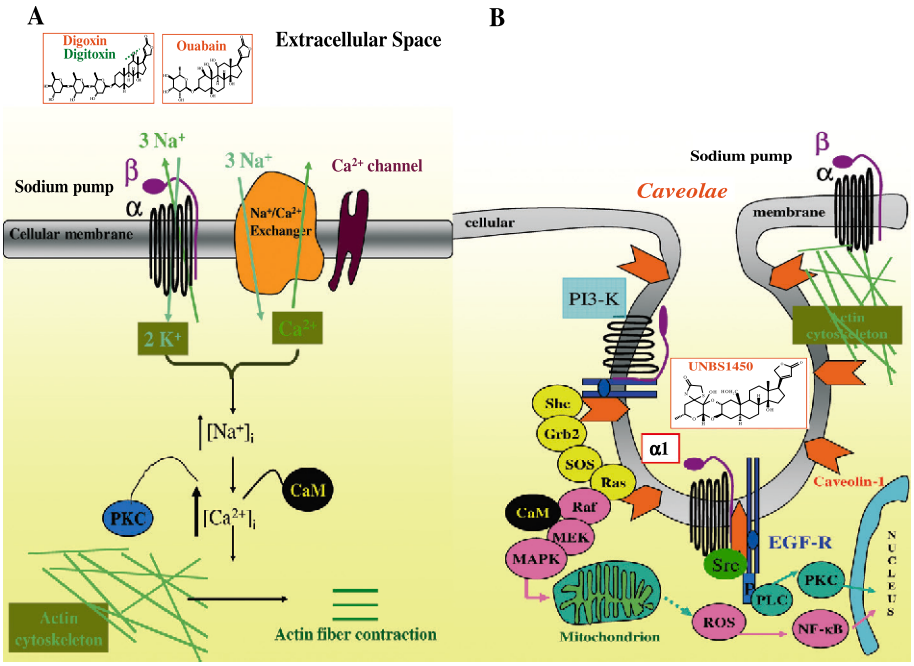

Fig. 4. The sodium pump functions as a receptor for cardiotonic steroid inhibitors. In addition to pumping ions (Na^+ and K^+) across the plasma membrane utilizing ATP as the driving force (A), the sodium pump in caveolae is engaged in assembly of multiple protein complexes that transmit signals to different intracellular compartments (B). (A) For every three Na^+ ions pumped out of the cell, two K^+ ions are pumped in. The partial inhibition of the sodium pump by the cardenolide ouabain causes a modest change in $[Na^+]_i$ and $[K^+]_i$, and a significant change in $[Ca^{2+}]_i$ via the Na^+/Ca^{2+}-exchanger. (B) The sodium pump signalosome closely interacts with major components of gliomagenesis: EGFR, caveolin-1, PI3K, Src and Ras. Upon ouabain binding, the Na^+/K^+-ATPase $\alpha 1$ subunit in caveolae associates with several proteins, such as caveolin-1 through two caveolin-binding motifs and Src via multiple domains. Activated Src secondarily trans-activates EGFR which in turn recruits the adapter protein Shc to relay signals to the Ras-Raf-MAPKs cascade. In contrast UNBS1450 at 10 nM, a concentration at which it demonstrates potent anti-proliferative and anti-migratory activity, does not elicit increases in $[Ca^{2+}]_i$ or $[Na^+]_i$ in cells but the compound decreases ($[ATP]_i$). *EGFR* Epithelial growth factor receptor; *PKC* protein kinase C; *PI3K* phosphoinositide 3′kinase; *Grb2* growth factor receptor bound protein 2; *Sos* son of sevenless; *Shc* src homology collagen-like protein; *PLC* phospholipase C; *MAPK* mitogen-activated protein kinase; *Ros* reactive oxygen species; *MEK* MAPK-ERK activating kinase

sodium pump is involved in controlling perturbations of Na^+ and K^+ homeostasis during apoptosis, and that anti-apoptotic Bcl-2 and Bcl-XL molecules influence these ionic fluxes.

Cardiotonic steroids: ligands of the sodium pump

Cardenolides and bufadienolides are the two chemical sub-classes that constitute the cardiotonic steroids [79]. The sodium pump is characteristically inhibited by cardiac glycosides. By binding to sodium pump, cardiotonic steroids elicit the activation of the so-called "Na^+/K^+-ATPase signalosome" [79] (Fig. 4B).

Cardenolides, such as digitalis (digitoxin and digoxin) have been used for the treatment of congestive heart failure for more than 200 years [79]. Digoxin is still used to treat approximately 1.7 million patients in the United States for heart failure and/or atrial fibrillation despite the development of newer pharmacological agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and β-blockers [79]. Besides its classical use in cardiac diseases, the use of digitalis in oncology has already been proposed [119]. As mentioned above the constitutive activation of the NF-κB pathway in cancer cells leads them to become chemoresistant [1, 4]. Different types of cardenolides are able to suppress the constitutive activation of NF-κB [73, 77, 78] to induce apoptosis [42, 78] and to overcome multi-drug resistance [125]. Several cardenolides have been shown to display *in vitro* anti-tumor activities against various types of cancer cells [42, 73, 77, 78, 119] including glioma cells [66]. However, none have ever reached clinical application because either their therapeutic index (ouabain, digitoxin) or their anti-tumoral activity (digoxin) were too low.

UNBS1450 is a novel cardenolide hemi-synthesized from 2″-oxovoruscharine [125], with a toxicity profile similar to digoxin but with significantly more marked anti-tumor activity [78]. It displays potent anti-tumor activity in human non-small cell lung cancers, especially in those cancers in which the sodium pump α1 subunit is over-expressed [78]. UNBS1450 induces non-apoptotic cell death in apoptosis-resistant cancer cells including lysosomal membrane permeabilization-related death in non-small cell lung cancer cells and autophagic cell death in glioblastoma cells [66].

The sodium pump is involved in cancer cell proliferation, migration and death

There are in fact two pools of the sodium pump within the plasma membrane with two distinct functions. One constitutes the energy transducing pool of the enzyme broadly distributed in the plasma membrane (Fig. 4A). The other is the signal transducing pool of the enzyme restricted to the caveolae which is independent of changes in intra-cellular Na^+ and K^+ concentrations [133] and requires the initial association of the sodium pump with tyrosine kinase Src [120] (Fig. 4B). The Na^+/K^+-ATPase signalosome closely interacts with major components of gliomagenesis, including for example, the interaction of EGFR

with caveolin-1 [133], the binding of PI3K to NaK [6] and the involvement of Src, Ras and EGFR in the signal-transducing function of NaK [120] (Fig. 4B).

The $\beta 2$ isoform of the sodium pump is in fact a homologue of the adhesion molecule on glia (AMOG) which is a recognition element for cell adhesion that subsequently links cell adhesion and ion transport [111, 113]. The AMOG/$\beta 2$ and the $\alpha 1$ subunits of the sodium pump come together to form functional sodium pumps [111]. AMOG is down-regulated in human and mouse gliomas [113]. We have identified the sodium pump as a major element in the migration of tumor cells [78, 79] including glioblastoma cells [66] arising from its close interaction with caveolin-1 and its role in the organization of the actin cytoskeleton in the caveolae. We have found that the $\alpha 1$ subunit of the sodium pump is located at the lamellipodia of the human glioblastoma cell line U373-MG, where it co-localizes with caveolin-1 [66]. Caveolae functions rely on caveolin-1, their major protein, which drives the formation of plasma membrane caveolae and anchors them to the actin cytoskeleton (Fig. 4B). In addition, caveolin-1 modulates cell interaction with the extra-cellular matrix, and brings together and regulates the interaction of different signaling molecules, with significant roles in cell movement [84]. Importantly, caveolin-1 depletion results in the loss of focal adhesion sites and overall cell adhesion [84]. Furthermore, we have shown by means of quantitative RT-PCR that the levels of $\alpha 1$ subunit mRNA are higher in glioblastomas (7/10 human glioblastomas analyzed) than in normal brain tissue (0/4 normal brain tissue samples) [66]. Such measurements also revealed high levels of the $\alpha 1$ subunit mRNA in human glioblastoma U373-MG cells [66].

We have shown that various types of cancer including glioblastomas [66], non-small cell lung cancers [78] and melanomas (manuscript in preparation) over-express the a1 subunit of the sodium pump when compared to the normal tissues from which they arise.

UNBS1450 is more potent in inhibiting the proliferation of U373-MG glioblastoma cells than that of normal cells [66], a feature that can be explained, at least in part, by the fact that (i) U373-MG glioblastoma cells express higher levels of sodium pump $\alpha 1$ subunits than normal cells, (ii) UNBS1450 decreases the intra-cellular ATP concentration ($[ATP]_i$) more markedly in U373-MG glioblastoma cells than in normal cells and (iii) $[ATP]_i$ is higher in normal cells than in U373-MG cancer cells [66].

Our results show that UNBS1450-mediated anti-proliferative and anti-migratory effects on human glioblastoma cells occur as a result of the disorganization of the actin cytoskeleton [66]. It should be borne in mind that the actin cytoskeleton is involved in many cellular processes that are essential for cell growth, differentiation, division, membrane organization and motility [5]. Moreover, the association of actin filaments with the plasma membrane provides mechanical stability, maintains cell shape and adhesion, and regulates

dynamic surface protrusions such as lamellipodia and filopodia, which are fundamental determinants of motility and migratory potential of cells [19].

Our strategy has been to target the $\alpha 1$ subunit of the sodium pump in those glioblastomas that over-express this subunit with novel, potent and selective cardenolides. In so doing using UNBS1450, it has been possible to markedly impair (at least in experimental models of human glioblastomas) both glioblastoma cell proliferation and migration (through a disorganization of the actin cytoskeleton), with marked features of autophagy as the terminal outcome. In essence, the targeting of the sodium pump $\alpha 1$ subunit in glioblastoma cells appears to impair both their proliferation and migration, even if they are resistant to apoptosis.

UNBS1450 has undergone regulatory preclinical evaluation (toxicology, safety pharmacology, drug metabolism and pharmacokinetic development studies are ongoing) and has reached Phase I clinical trials in Belgium and the Netherlands.

Brain tumor stem cells a potential target to combat malignant glioma

Cancer stem cells are thought to be crucial for tumorigenesis [109]. The brain tumor stem cell hypothesis proposes the existence of multipotent glioma cells of origin that are characterized by the expression of stem cell markers, by the capacity for self-renewal, multilineage differentiation, re-establishment of tumor after transplantation and resistance to radiotherapy and chemotherapy [18, 127, 109]. Therefore, the eradication of brain tumor stem cells is essential for long-term brain tumor remission after treatment. Gilbertson and Rich recently reviewed data showing that stem cells of glioblastoma are found in intimate contact with the aberrant tumour vasculature [29]. These cancer stem cells can secrete diffusible factors such as VEGF, which recruit aberrant tumor vasculature to the niche. In turn, tumor vasculature and other glioma cells secrete factors that maintain aberrant cancer stem cell self-renewal. Recent results show for the first time that brain tumor stem cells are susceptible to adenovirus-mediated cell death via autophagy *in vitro* and *in vivo* [45]. Because adenoviral proteins can completely overcome the molecular machinery of the infected cell, the authors hypothesized that Delta-24-RGD, an oncolytic adenovirus with enhanced tropism to glioma cells and selective replication in cancers cells with an abnormal Rb pathway [25], may act as a potent therapeutic agent to target brain tumor stem cells and prevent them from developing resistance to standard adjuvant therapy. The authors showed that Delta-24-RGD induced the formation of acidic vesicular organelles associated with an increase in the membrane-bound MAP1LC3-II protein, a modification that is essential for the formation of autophagosomes, without an increase in the

levels of beclin1 (Atg6) in several glioma treated stem cell lines (Fig. 3). By contrast, the protein levels of Atg5, a key molecule in the conversion of LC3-I to LC3-II and therefore required for autophagosome formation and autophagic cell death, were dramatically increased. Immunofluorescence analyses of the brains of nude mice bearing xenograft tumors and treated with intratumoral injections of Delta-24-RGD identified high levels of expression of the proautophagic protein Atg5 in the tumor area adjacent to the necrosis. No other area in the tumor or any area of untreated tumors was positive for Atg5. Therefore, the *in vivo* assessment of adenovirus-induced autophagy by means of Atg5 may be a useful way to monitor oncolytic adenovirus efficacy in future clinical trials [45]. More recently, the same group has shown that Delta-24-RGD in combination with RAD001 (everolimus, an mTOR inhibitor) induced enhanced antiglioma effect via autophagic cell death [2].

Conclusions

The treatment of glioblastomas requires a multidisciplinary approach that takes the presently incurable nature of the disease into consideration. Treatments are multimodal and include surgery, radiotherapy and chemotherapy. Current recommendations are that patients with glioblastomas should undergo maximum surgical resection followed by concurrent radiation and chemotherapy with the novel alkylating drug temozolomide, and this in its turn to be followed by additional adjuvant temozolomide for a period of up to 6 months. However, glioblastomas almost invariably recur near their initial sites. Disease progression usually occurs within 6 months and rapidly leads to death. A number of signalling pathways can be constitutively activated in migrating glioma cells, thus rendering these cells resistant to pro-apoptotic insults such as conventional chemotherapies.

However, a number of strategies are emerging to overcome, at least partly, the resistance of migrating glioma cells to apoptosis. These involve (i) inhibition of the molecular pathways involved in apoptosis resistance that are overexpressed in glioma cells, (ii) induction of autophagy in glioblastoma cells as well as in glioma stem cells and (iii) reducing malignant glioma cell migration; a process which in turn seems to restore a certain level of sensitivity to pro-apoptotic cytotoxics in migration-restricted glioma cells.

Control of glioblastomas by topical therapy applied to the resection cavity during surgery may reduce the rate of local failure and increase the time for local tumor progression. New local agents including targeted pro-autophagic therapies as well as advances in delivery systems including CED are likely to play a role in the future trial for migrating glioma cells.

Until recently, the new treatments for malignant gliomas have focused largely on the intrinsic properties of glioma cells with the targeted therapy.

Given the disappointing results from these clinical trials, it seems clear that novel biomarker-guided clinical trial designs are needed. One such trial design uses a pharmacodynamic marker to monitor the efficacy of a given therapeutic agent. A recent series of studies have supported the concept that malignant gliomas might to be seen as an orchestration of cross-talk between cancer cells, micro-environment, vasculature and cancer stem cells. Successful treatment of invasive brain tumors will depend on blending cocktails of targeted agents that are tailored for an individual patient.

It is hoped that novel therapies derived from a cellular and molecular understanding of glial tumorigenesis and of the interaction between these cancers and their micro-environment, and advances in non-invasive diagnosis, surgical technology and adjuvant treatment will significantly improve the clinical outcome of these devastating lesions.

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Deep brain stimulation for psychiatric disorders – state of the art

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With 3 Figures and 4 Tables

Contents

Abstract

A substantial number of patients suffering from severe neuropsychiatric disorders do not respond to conventional therapeutic approaches. Results

from functional neuroimaging research and the development of neuromodulatory treatments lead to novel putative strategies. Recently, one of those methods, deep brain stimulation (DBS) has been applied in selected patient with major depression and obsessive-compulsive disorder (OCD) and major depression.

We summarize in this review, the state of art of knowledge about the neurobiology of depression and OCD and historical treatment methods. Principles of DBS and reasons for the use of DBS in neuropsychiatry are discussed. Different targets have been chosen in a hypothesis-guided way and first results have demonstrated that DBS might be able to modulate dysfunctional neural networks in both major depression and OCD. Although DBS is a unique and promising method for otherwise treatment resistant psychiatric patients, mandatory treatment standards have to be applied for patient and target selection. Therefore, a distinct focus of this review lies on ethical aspects for DBS in neuropsychiatric disorders.

Keywords: Deep brain stimulation (DBS); depression; obsessive compulsive disorders; neuroethical aspects.

Introduction

Today, different well established forms of drug treatment and psychotherapy are available for the treatment of neuropsychiatric disorders, alone or in combination they are effective in most patients [4, 37]. However, there remain a sizable number of patients that cannot be helped with these interventions. Indeed, 8–13% of patients suffering from major depression have a poor outcome after five years of treatment [31]. A more recent study found that 63.2% of patients included in the STAR-D study were not treated to remission in the acute study phase [49]. These patients are called "treatment-resistant" and have been treated with several antidepressants (e.g., tricyclica, selective serotonine reuptake inhibitors) augmentation agents (e.g., lithium, neuroleptics), psychotherapy and often electroconvulsive treatment. In obsessive-compulsive disorder (OCD) the number of treatment-resistant patients is estimated to be 10–40% [30, 16]. These patients have little hope of recovery, are almost always stigmatized and remain in a state of extremely poor quality of life. Treatment resistant psychiatric disorders are a significant source of worldwide disability [43]. Thus, it clearly is a moral imperative to develop alternative treatment methods for these patients.

In this review, we will outline putative new options for treatment-resistant depression and OCD. A special focus lies on the establishment of mandatory research guidelines.

History of deep brain stimulation

Directly neurosurgical interventions for psychiatric indications have a long and somewhat tainted history [34]. Psychiatric neurosurgery began in the 30s of the last century when Egas Moniz performed the first frontal lobotomy [42]. This method was further developed and widely used in the 1940s, when Freeman and Watts performed frontal lobotomies lacking any other treatment for severe mental disorders [13]. These operations were crude, not guided by scientific hypotheses, were associated with high mortality and lead to unacceptable adverse effects. With the invention of psychotropic drugs in 1954 and their broad application, the interest for surgery waned [13]. Due to severe side effects of psychopharmacological medications and the availability of new operating techniques (stereotactic surgery), interest in functional neurosurgery for psychiatric disorders returned [13]. Today, stereotactic operations allow reaching a target precisely with minimal lesions and minimal side effects. Methods are cingulotomy (bilateral lesioning of cingulate gyrus) for OCD, major depression and pain disorders [25, 55], capsulotomy (anterior limb of the internal capsule as relay between cortex and thalamus) for OCD, subcaudate tractotomy (interrupts cortical pathways to striatum and to thalamus) for OCD and depression [25, 55] and limbic leucotomy (combination of cingulotomy and a ventral lesion similar to that of subcaudate tractotomy) for OCD, depression and self-mutilation [25, 47, 55]. The efficacy of neurosurgery for otherwise therapy resistant patients lies between 30 and 70%, depending on the disorder and the selected target [13].

Electric stimulation of the brain probably had its beginnings in 1879, where limb movement were elicited by stimulating the motor cortex in dogs, human studies followed in 1884 [22]. The first chronic brain stimulation was performed in the mid 20th century, when the Nucleus Caudatus was stimulated for eight weeks in a case of a severe depressed patient [17].

Insights from lesioning studies, imaging studies and animal models have contributed to the development of deep brain stimulation (DBS). Adams was a very early pioneer who stimulated the internal capsule for relief of chronic pain [2]. The technique of chronic DBS used today was invented in the 80s by Benabid and coworkers for the treatment of movement disorders [10]. Today, this method is clinically used for the treatment of tremor associated with Parkinson's disease, chronic pain and dystonia. The observation of induced psychiatric side effects (e.g., changes in mood, hypomania, reduction of anxiety) gave the impulse to try DBS also for psychiatric disorders [36]. Another impulse was the fact that the effective but irreversible ablative neurosurgical interventions could now be emulated using DBS with a focused, fully reversible and titratable technique (see Fig. 1). Insights from a somewhat different method of electric brain stimulation (vagal nerve stimulation) further encouraged the development of DBS [52].

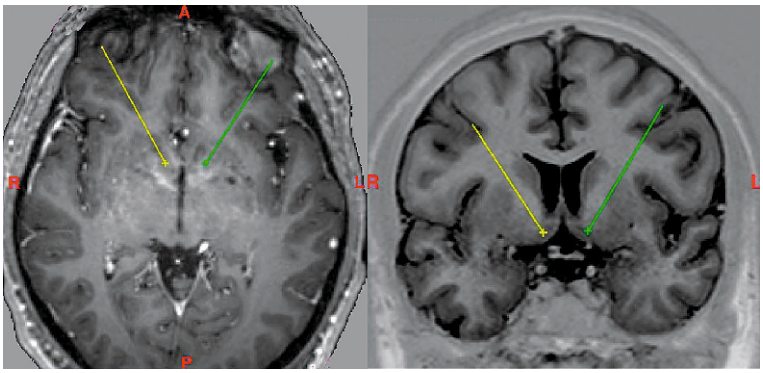

Fig. 1. Actual location of the electrode leads in the post-operative control X-ray in a DBS study for depression [54]

Principles of DBS

Deep brain stimulation is achieved by an implanted, battery powered neurostimulator, placed subcutaneously usually in the chest area. One or two leads connect to the actual stimulating electrodes in the brain. The exact neurobiological mechanisms by which DBS exerts modulatory effects on brain tissue are not yet fully understood [26]. On the neuronal level, excitatory and inhibitory processes might play a role [40]. It has been suggested, that DBS leads to a functional lesion of the surrounding tissue. Depolarisation blockade of current dependent ion channels [12], exhaustion of the neurotransmitter pool [66] or synaptic inhibition [15] are suggested mechanisms of action. Neural activation in the stimulated areas has been described as well [28].

It is unknown which part of the neuronal structure (e.g., cell body, axon) is primarily modulated by DBS. The effect of DBS on neurons obviously depends on different factors: the physiological properties of the surrounding brain tissue, the geometric configuration of the electrode as well as the distance and orientation of the neuronal elements towards the electrode [32]. Stimulation parameters (frequency, amplitude, pulse width, duration) also clearly have an impact on the effect: a nonlinear relationship between stimulus duration (pulse width) and amplitude (voltage/current) has been observed [48]. Thus, the stimulation volume is not a fixed area around the electrode and the effect on neuronal tissue is variable. With commonly used parameters, a relatively large volume of neural tissue is influenced [32].

Neurophysiologic recordings during stimulation in patients with movement disorders have demonstrated, that the oscillatory activity occuring between cortex and midbrain is modulated by DBS [32]. Changes in neurotransmitter release (Glutamate, Dopamine) have been reported in some studies [27, 59].

Functional neuroimaging data have demonstrated that DBS changes the activity of brain areas far beyond the targeted region. Thus, complex neural

networks are modulated [32, 39, 56, 60]. These results go well in line with the long-term changes described in psychiatric patients.

In summary, effects of DBS crucially depend on the target and the stimulation parameters. Short time processes might well explain acute effects in movement disorder. Especially in psychiatric disorders, long-term changes in symptoms have been described. This can only result from long-lasting, complex modulation of neural networks [40].

Neurobiology of depression and OCD

Neurobiology of depression

Symptoms of depression include sadness, lack of interest and motivation, anhedonia, disturbances in sleep and appetite, hopelessness, suicidal thoughts, psychomotor slowing and the feeling of guilt as well as cognitive deficits. Major depression can be conceptualized by the interaction of genetic, neurobiological, environmental and psychological factors [9]. The relevance of transmitters (e.g., Serotonine, Noradrenaline and Dopamine) has been shown [11]. Family studies point to the involvement of several genes in the genesis of depression, for example genes for glucocorticoid receptors and for brain-derived neurotrophic factor [57] as well as circadian genes [11]. However, up to today evidence of the involvement of specific genes is less than convincing. Life events and daily hassles clearly are examples of psychological factors contributing to the etiology of depression [58].

In contrast to neurological disorders, the pathological interplay of several brain regions contributes to the development of this disease. Metabolic studies suggest that different symptoms are mediated by different brain regions [65]. A network-model of depression that integrates biochemical, electrophysiological, imaging and animal studies, has been described by Mayberg [38]. According to this model, depression results from a dysregulation of limbic-cortical connections: pathological changes in dorsal brain regions (including the dorsolateral prefrontal cortex, inferior parietal cortex and striatum) were associated with cognitive symptoms (e.g., apathy, anhedonia, hopelessness, deficits in attention and executive function), changes in ventral areas (hypothalamic-pituitary-adrenal axis, Insula, subgenual cingulate and brainstem) contribute to the vegetative and somatic aspects of depression (e.g., sleep disturbance, appetite, endocrine dysregulation). This model underlines the role of the rostral cingulate cortex in regulating the network [38]. The involvement of further regions in depression are discussed: the hippocampus contributes to memory deficits, the nucleus accumbens was associated with anhedonia and lack of motivation, the amygdala plays a role in the processing of aversive stimuli and avoidance [11] (see Fig. 2). Animal and imaging data point towards an involvement of the habenula

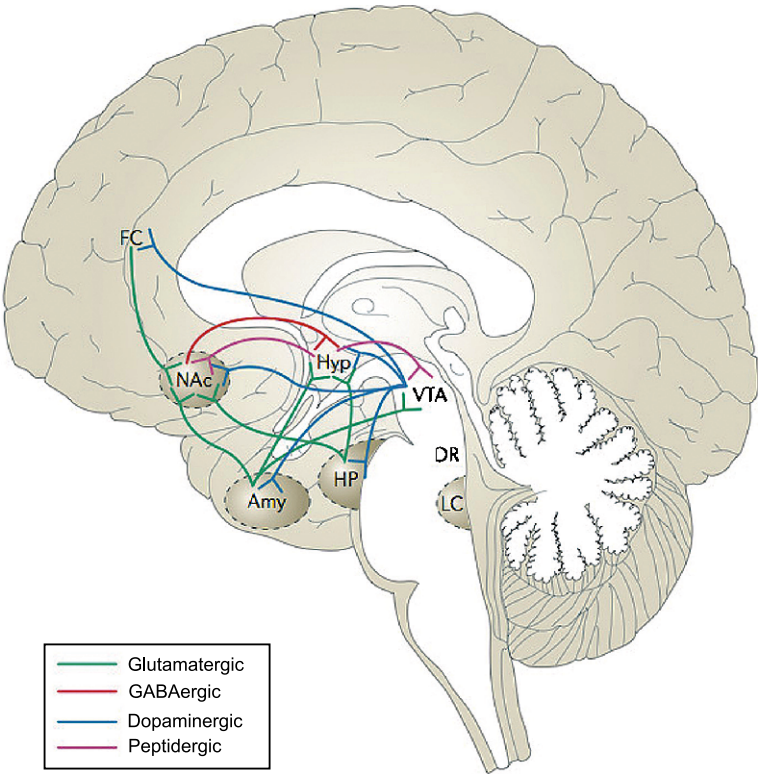

Fig. 2. Circuit of mood in depression [11]

in depression: Sartorius and Henn [50] suggested that overactivation of the lateral habenula leads to down regulation of serotonergic, noradrenergic and dopaminergic systems and stimulation of the hypothalamic-pituitary-adrenal axis in depression.

Neurobiology of OCD

OCD is characterized by anxiety-provoking thoughts (obsessions) and repeated, time-consuming behaviours (compulsions) [61]. As in most psychiatric disorders, a complex interplay of genetic factors, neurotransmitter changes and psychosocial characteristics contribute to the development of this disease. Changes in dopamine and serotonine have been reported [61]. Dysfunctions in a network connecting the cortex and basal ganglia are supposed to underlie OCD. Probably, overactivation of the direct pathway of the cortico-striatal-pallidal-thalamic-cortical loop lead to intrusive thoughts and other OCD symptoms [8] (see Fig. 3). Imaging data demonstrated changes in orbitofrontal cortex, anterior cingulate cortex and caudate nucleus in OCD [7].

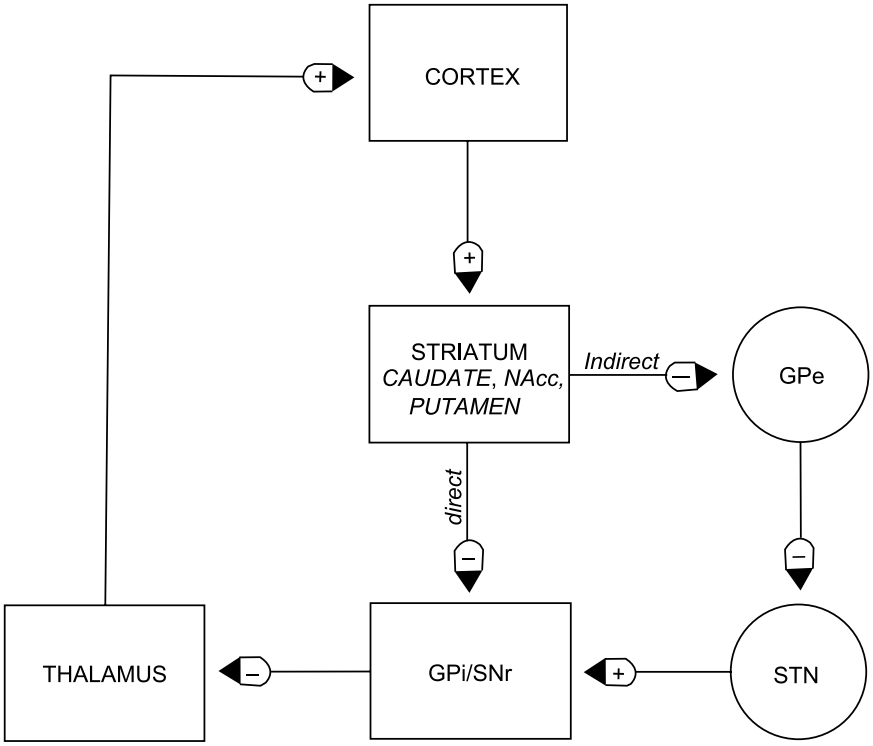

Fig. 3. Circuit of OCD [35]

Studies of DBS and psychiatric disorders

Problems in target selection

Hypotheses-guided search for a target is fundamental in DBS studies. In psychiatric disorders, targets have been chosen in a hypothesis guided way using knowledge derived from lesion and imaging studies as well as from current understanding of the pathophysiology of the respective disorder. In the contrary to neurological diseases, there is not a single pathological structure in psychiatric illness. Several brain structures presumably play different roles in the development as well as in the maintenance of symptoms. Some targets are in close anatomical or functional relationship (neural networks) and an overlap of effect is plausible. Thus, different targets might manipulate the pathological network at different nodes. It has been shown, that several targets can lead to remission.

Targets in depression

DBS has been applied to the subgenual cingulate cortex (Brodman Area cg25) [39]. This region has probably dysfunctional connections to the dorsal and

ventral compartments of the emotion regulation circuit in depression [38] and plays a critical role in remission. Mayberg and colleagues could demonstrate, that two months after surgery, 5/6 patients met the response criterion (baseline score in the Hamilton Depression Rating Scale (HDRS) minus 50%), after 6 months, four patients showed sustained response [39]. Different neuropsychological parameters that were impaired at baseline were significantly improved. A reduction in the pathological hyperactivity in this region has also been demonstrated using Positron Emission Tomography (PET) in this study. During the blinded sham stimulation phase ($n = 1$), the patient's condition worsened considerably. No adverse events due to stimulation were observed [39].

Another group studies the effect of DBS in depression using as target the anterior limb of the capsula interna. Historic lesion studies contributed to the hypothesis that the inactivation of larger brain areas inhibits dysfunctional connections through this region. After one month, there has been a substantial reduction in depression in the majority of patients patients, reflected in the Montgomery-Asberg Depression Rating Scale. This outcome remained stable with some fluctuation over half a year [23].

Table 1. *DBS targets for major depression*

Target	Hypothesis	Hypothesis based on
Anterior Gyrus Cinguli (Brodman area Cg25)	Inactivation of Cg25 leads to recovery	Functional neuroimaging findings
Anterior Limb of Capsula Interna	Inactivation of dysfunctional connections	Clinically effective neurosurgical interventions for OCD and depression
Nucleus Accumbens	Modulation of the Nucleus Accumbens, which is a central structure in the reward system, leads to improvement of anhedonia	Clinical experience neurobiology of reward system
Habenula	inhibition of the lateral Habenula leads to upregulation of serotonergic, noradrenergic, dopaminergic system and downregulation of HPA axis	Functional neuroimaging findings animal studies
Thalamus	Dysfunctional connection between thalamic system and orbitofrontal in depression Disruption of overactivation of frontal cortex with DBS	Functional neuroimaging findings animal studies

Table 2. *DBS studies in major depression*

Reference	*n*	Comorbidity	Target	Study design	Stimulation parameters	Effect	Side effects
[39]	6	not reported	anterior cingulate gyrus (Cg 25)	systematic parameter search acute off-on-off-on trials, blinding phase, 6 months follow-up	monopolar stimulation 130 Hz 60 μs voltage increased to 9 V at each contact mean parameters at 6 months: 4 V, 130 Hz, 60 μs	Remission of depression in 4/6 patients, all patients reported acute effects, one patient met response criteria during first 4 months, normalization of brain metabolism in Cg25	dose-dependend adverse effects (lightheadedness, headache, psychomotor slowing) at high local skin irritations (2/6) due to which the system needed to be explanted skin pressure necrosis (1/6)
[5]	1	OCD	Ventral N. Caudatus (contacts 2, 3), N. Accumbens (contacts 0, 1)	six months observation, no blinding phase		Remission of depression (HDRS $<$ 7); stimulation of all contacts necessary	failure of the pulse generator battery improved visual and verbal memory
[29]	1	Borderline personality disorder, bulimia nervosa	Lower Stem of Thalamus	24 months observation, blinding phase	2.5 V, 130 Hz, 450 μs	Remission of depression, (Decrease of HDRS from 42 to 10)	transient decrease in learning-to-learn capabilities (WCST) improvement in verbal and nonverbal memory and abstraction tests
[54]	3	none	Nucleus Accumbens	3 months observation		Reduction of anhedonia ratings, Normalization of brain metabolism in N. Accumbens	

We selected the Nucleus Accumbens as target for DBS because of its prominent role in the reward system. We could demonstrate, that modulation of this structure was associated with changes in the symptom of anhedonia and mood in 3 depressed patients [54]. Stimulation current correlated negatively with anhedonia ratings. Normalization of brain metabolism in frontostriatal networks as result of stimulation was also observed [54]. No side effects due to stimulation occurred. Results from a total of ten patients in this study show acute as well as long-term antidepressant effects of DBS at this target [14].

Two single-case studies in OCD patients with comorbid depression have shown antidepressant effects at different targets:bilateral stimulation of the ventral nucleus caudatus in combination with Nucleus Accumbens for OCD lead to remission of depression (HDRS_17 $<$ 7) after six month. No neuropsychological deterioration was reported [5].

Bilateral stimulation of the lower thalamus stem also lead to remission in one depressed patient (HDRS 42 $\rightarrow$ 10). The effect remained stable for 24 months [29]. During blinded discontinuation of stimulation, the patient's condition aggravated. The lower thalamus stem is the connection between unspecific thalamic system and orbitofrontal cortex. Dysregulation of this system seem to play an important role in the development of depression [29].

The habenula has been proposed recently as target for DBS in depression by Sartorius and Henn [50]. Animal data and imaging studies have shown, that this regions controls serotonergic fibers from the dorsal raphe nuclei and noradrenergic fibers from the locus coeruleus. The authors hypothesize that over activation of the habenula is related to depression [50].

In summary, five different targets sites are currently under research for DBS in depression therapy. Due to very small sample sizes, it cannot be decided about most effective target sites yet. First results have shown sustained antidepressant effects, making DBS a putative therapy option for treatment-resistant depression (see Tables 1 and 2).

Targets in OCD

In OCD, there have been proposed different targets according to the underlying pathological network (see Table 3). The orbitofrontal cortex and the anterior cingulate cortex are part of the OCD circuit. Unfortunately, these regions are very large and not well circumscribed in relation to this disease. Thus the size of cortex region that needs to be modulated would be too large [35]. In most studies, the anterior limb of the internal capsule was the target for either unilateral or bilateral stimulation [1, 3, 21, 44, 46, 62]. All studies reported on promising results ranging from response to complete remission (see Table 4). In terms of side effects, some studies reported on induced, directly stimulation

Table 3. *DBS target sites for OCD*

Target	Hypothesis	Hypothesis based on
Ventral/anterior Capsula Interna	Relay between Cortex and Thalamus	Anterior capsulotomy
N. Caudatus	modulates both direct and indirect OCD pathways	Subcaudate tractotomy Volumetric studies Metabolic studies Imaging studies
N. Subthalamicus–N. Accumbens	Modulates indirect OCD pathway overactivation of the direct pathway provokes OCD symptoms	Imaging studies Imaging studies

related symptoms of hypomania which all ceased completely after reduction of stimulation intensity [24, 44, 46].

The Nucleus thalamicus- zona incerta has been studied at three patients with Parkinson's disease and comorbid OCD [18, 36]. Both studies reported considerable amelioration of OCD symptoms. The Nucleus Accumbens and Nucleus Caudatus were target in one case study with comorbid depression (see above) [5]. This patient achieved remission status [5]. Unilateral stimulation of the N. Acc lead to good results in 14 implanted patients [33]. Stimulation of the ventral capsule/ventral striatum lead to major improvement in 50% of the patients [24]. Side effects related to the stimulation were transient hypomania and increased anxiety which could be counteracted by parameter change [24].

In summary, there are promising effects for different targets, but as worldwide sample sizes are small, it is too early to select one favourable target if there is any. As OCD is a heterogeneous disease, there might be different optimal targets for different symptom clusters.

Safety and advantages of DBS

In DBS, complications are either related to the operation itself (e.g., bleeding, local infections at the chest) and transient side effects are related to the stimulation (e.g., elevation of mood, anxiety, motor slowing). Fortunately, the safety of the stereotactic operation technique has been extremely improved in the last years with the help of neuroimaging. Bleeding rate of DBS surgeries are between 0, 2 and 5% [33]. It has to be underlined, that no side effects such as extrapyramidal effects, weight gain, that substantially effect compliance, are reported.

On the other hand, DBS has many advantages over traditional therapy methods: clinical effects can be achieved without irreversible lesioning, stereotactic operation is the most minimal neurosurgical method and electrodes can be completely removed if necessary. Brain activity can be changed in a direct, controlled manner.

Table 4. *DBS studies OCD*

References	*n*	comorbidity	Target	Study design	Parameter	effect	Side effects/problems
[44, 46]	6	Somatoform disorder, major depression, histrionic and narcistic personality disorder	Anterior Capsule	Double blind; on-off for 3 months (4 patients), 21 months follow-up,	Different parameters individually adjusted, up to 10.5 V, 100 Hz, 450 μs	66% of patients responded; acute effect in one patient (reduced anxiety, depression, and obsessive thoughts), worsening in stimulation-off-phase	Sensation of the leads and the stimulator fatigue, acute worsening of anxiety with some parameters, weight changes, at high amplitude: cognitive and behavioural disinhibition (reversed when stimulation amplitude was decreased) short battery life (5 months)
[36]	2	Parkinson's disease	N. Sub-thalamicus	Clinical observations one month before surgery and after 6 months	Pt1: 3 V, 185 Hz, 60 μs; Pt2: 3 V, 130 Hz, 90 μs	58% improvement in patient 1, 64% improvement in patient 2 in Y-BOCS after 2 weeks	
[3]	1	Axis II: deferred	Anterior Limb of Capsula Interna	Case study; parameters set at 2 weeks after implantation, reviewed at 6 weeks and 3 months	At 2 weeks: 2 V, 100 Hz, 210 μs	Positive case report; decrease in Y-BOCS from 34/40 to 7/40	

(*continued*)

Table 4 (*continued*)

References	*n*	comorbidity	Target	Study design	Parameter	effect	Side effects/problems
[21]	3	Somatoform disorder	Anterior Capsule	15–33 months follow-up	High amplitude	66% of Patients responded	
[62]	4		N. Accumbens	Clinical observations, 24–30 months follow-up	2–6.5 V	75% of patients responded	
[5]	1	Major depression	N. Caudatus/ N. Accumbens	Case study 15 months follow-up	Stimulation intensity increased → 2 V, 130 Hz, 90 μs (deepest contacts used bilaterally) two upper contacts added and voltage increased up to 4 V and 120 μs	Positive case report; remission of depressive symptoms at 6 months; delayed remission of OCD at 12–15 months	
[18]	1	Parkinson's disease	N. Sub-thalamicus	Case report six months follow-up	Left electrode: 3.5 V, right electrode: 1,3 V; 185 Hz, 60 μs Chronic monopolar stimulation	positive case report, PD motor symptoms improved, OCD symptoms disappeared, decreased anxiety	

(*continued*)

Table 4 (*continued*)

References	*n*	comorbidity	Target	Study design	Parameter	effect	Side effects/problems
[1]	4	MD (3/4), social phobia, past anorexia, bulimia	Anterior Capsule	Double-blind for 2×3 weeks, open label testing phase, 4–34 months follow-up	5–10.5 V, 4–23 months follow-up	25% of patients responded	one suicide, judged to be unrelated to stimulation
[24]	10	Major depression (8/10)	Ventral Capsule/ Ventral Striatum	Patients were blinded	Intraoperative: Different parameters, Best results: ventral contact (0 and/or 1) negative, 100–130 Hz, 90–210 μs, 8–17 mA	50% of patients responded (YBOCS scores and level of global functioning)	*Implantation*: intracerebral hemorrhage after lead insertion, a single tonic-clonic seizure, superficial surgical wound infection, all treated successfully, *stimulation*: acute effects on mood (increased anxiety); *mood elevation/hypomania*: increased energy, speech production, social interactions; DBS interruption (due to battery depletion): worsening in depressed mood and OCD symptoms; Empty batteries after 5.5–13 months, one patient died due to recurring breast cancer

Furthermore, DBS offers the opportunity to continuously adjust stimulation variables for each patient in order to optimize therapy. The patient can turn off stimulation immediately if side effects occur. DBS is the only neurosurgical method that allows blinded studies for therapy control.

Thus, DBS is an exciting method and offers unique possibilities to gain more insight into the underlying neurobiology of psychiatric disorders.

Ethical aspects and standards in DBS

Ethical considerations

Referring to the difficult history of psychosurgery, there have to be applied the highest ethical standard for DBS. High mortality, immense suffering and low quality of life as well as the social burden are in favour for the use of this method for therapy-resistant patients. In addition, the potential benefit for the understanding of pathological principles in mental disorders is high. Nonetheless, some ethical aspects have to be considered more closely [19, 20, 53, 63, 64].

The following fundamental ethical concerns are mostly applicable for all clinical interventions (e.g., pharmacotherapy, psychotherapy) as well as for DBS in neurological disorders: are patients able to give confirmed consent? It has been demonstrated, that depressed patients showed few impairments in their ability to give informed consent to participate in research [6]. Another question is, how far should we manipulate human nature [20]? Especially long-term effects of DBS cannot be evaluated yet, but in comparison to pharmacotherapy, brain stimulation is a more specific and reversible intervention. So far, there are no harming effects (or changes in personality) reported. Most people would agree that trying to heal illnesses is a fruitful manipulation of human nature. More problematic is the danger of misuse, e.g., for mind control or for over enhancing normal (healthy) cognitive functions (neuro enhancement) [19, 20]. As clinical researchers on therapeutics in psychiatry, our aim is to help patients to lead a normal life which implies normal cognitive function and autonomy of the patient.

Practical ethical issues are the availability of alternative treatment options (e.g., pharmacotherapy, ECT, psychotherapy). As this method is only applied to treatment-resistant patients, there is no hope of other treatment approaches currently available.

The reversibility of the method and the potential benefit are strong ethical arguments for the use of DBS in psychiatric disorders [63, 64].

On the other side, there are substantial risks (bleeding, infection, etc.) and the efficacy is not yet established. Thus, each case has to be evaluated carefully and obligatory ethical standards have to be established in form of inclusion and exclusion criteria. This also prevents researcher to “jump on the bandwagon”.

In summary, it would be unethical to abandon a possible beneficial method before its scientific evaluation only for historical reasons. Until this method will be scientifically evaluated, obligatory standards for patient inclusion and the selection of targets have to be established.

The path towards mandatory standards for DBS in psychiatric disorders

The different ethical aspects discussed above lead to the proposal of criteria for the application of DBS. In 2002, Nuttin and colleagues have put forward minimum requirements for the use of DBS in psychiatric diseases [45]. These include an ethics committee that approves the study protocol and oversees the ongoing project. They also propose a committee for the patient selection. It is questionable, if a committee with limited access to the individual patient should make this decision or if an external gate keeper who is not involved otherwise in the study, is more suitable for this task. It has to be taken into account that in case of patient selection, responsibility cannot be shared.

According to Nuttin and colleagues, inclusion criteria are severity, chronicity, disability and treatment refractoriness [45]. These criteria need to be further specified for each disease. Mink and colleagues already developed some for Tourette disorder [40]. Our group applied the following criteria [51]:

Inclusion criteria:

- Major depression (MD), severe, unipolar type German mother tongue:
- Hamilton Depression Rating Scale (HDRS24) score of >20:
- Global Assessment of Function (GAF) score of <45:
- At least 4 episodes of MD or chronic episode >2 years:
- 5 years after first episode of MD:
- Failure to respond to *adequate trials (>5 weeks at the maximum recommended or tolerated dose) of primary antidepressants from at least 3 different classes:
  - Adequate trials (>3 weeks at the usually recommended or maximum tolerated dose) of augmentation/combination of a primary antidepressant using at least 2 different augmenting/combination agents (lithium, T3, stimulants, neuroleptics, anticonvulsants, buspirone, or a second primary antidepressant);
  - an adequate trial of electroconvulsive therapy [ECT] (>6 bilateral treatments); and
  - an adequate trial of individual psychotherapy (>20 sessions with an experienced psychotherapist).
- Able to give written informed consent
- No medical comorbidity
- Drug free or on stable drug regimen at least 6 weeks before study entry

Exclusion criteria:

- Current or past nonaffective psychotic disorder
- Any current clinically significant neurological disorder or medical illness affecting brain function, other than motor tics or Gilles de la Tourette syndrome
- Any clinically significant abnormality on preoperative magnetic resonance imaging (MRI)
- Any surgical contraindications to undergoing DBS
- Current or unstably remitted substance abuse (aside from nicotine)
- Pregnancy and women of childbearing age not using effective contraception
- History of severe personality disorder

Another important aspect of quality in DBS research is patient management: clinical experience has shown that it is extremely important to clarify the patient's expectations before surgery, and to closely follow the patients after the operation in order to avoid stress, catastrophic thinking, hypomania or suicidality, especially in case of suboptimal acute therapy effect. In case of no response, hospitalization or other treatment options (change in medication, ECT, psychotherapy) should be offered.

Some issues have to be taken into account regarding the adjustment of stimulation parameters: as a broad variety of possible settings is available and there usually is not an immediate response, but changes need several weeks, parameters should be changed only after several weeks. This can be compared to pharmacotherapy. With parameter changes, all other therapies should be kept constant.

The quality of the research team is also one main factor in DBS therapy: patient selection, baseline psychiatric and neuropsychological assessment and the operation and follow-up requires a team of surgeons, psychiatrists and neuropsychologists which are experts in the field of the respective disease. Each case has to be documented according to scientific standards (standardised diagnostic with clinical scales, evaluation of cognitive parameters with psychological tests, report of parameter changes, other therapies, additional neuroimaging etc.). These requirements can only be fulfilled in special academic centres where all these resources are available. Fundamental guidelines for study design should also be agreed on (e.g., randomized controlled trials? Blinding phase? Period for follow-up?). Last but not least, standards for target selection also need to be established (e.g., strong anatomical and functional hypotheses). It is our task as neuroscientists together with legal authorities to work out standards to guarantee for the quality of research in this field.

Conclusions

A substantial percentage of therapy-resistant psychiatric patients require new therapy approaches. Deep brain stimulation offers the possibility to manipulate

pathological neuronal networks in a very precise way. First studies showed very promising effects in depression and OCD. There are no fundamental ethic objections to its use in psychiatric disorders, but until substantial clinical data is available, mandatory standards are needed for patient and target selection, quality of research centre and study protocol.

The future of DBS

DBS is a unique and very promising method for the treatment of therapy-resistant psychiatric patients. Nonetheless, the duration of the battery limits the choice of stimulation parameters, increases the risk of infection and raises treatment costs. Rechargeable batteries are currently under development. Actual technology allows mainly continuous stimulation with little possibility for dynamic adjustment. Recording signals from the DBS electrode and combining DBS with imaging in order to map the spatiotemporal unfolding of DBS-elicited whole brain activity are rich research tools. Imaging techniques can be used with DBS to reveal the fundamental mechanism of pathological brain function.

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Standards

High flow extracranial to intracranial vascular bypass procedure for giant aneurysms: indications, surgical technique, complications and outcome

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Contents

Abstract

High flow extracranial–intracranial (hfEC–IC) vascular bypass remains an important surgical technique in selected patients. For example, in those with

giant aneurysms where the natural history of the condition is poor, and direct surgical approaches are recognised as excessively hazardous. hfEC–IC also allows for major carotid vessel occlusion in the treatment of skull base tumours which would otherwise be untreatable. We describe the indications, techniques, complications, and outcomes of this procedure in an era where few neurosurgeons are exposed to high volume vascular neurosurgery, and fewer still are trained to perform hfEC–IC. We emphasise the need for a stereo-typed and meticulous technique, highlighting key points at each stage of the operation, to ensure graft survival and minimal chances of morbidity.

Keywords: Giant aneurysm; high flow EC–IC bypass.

Introduction

The aim of this chapter is to outline the current indications, techniques, complications and outcomes of high flow extracranial–intracranial (hfEC–IC) bypass for extreme cerebral vascular disease.

hfEC–IC is a procedure that results in the formation of a sizable vascular conduit between the extracranial circulation and the intracranial circulation, allowing the opportunity to sacrifice a major intracranial parent vessel. The method continues to be recognised as technically demanding with significant hazards, all the more pertinent given reduced training opportunities in vascular neurosurgery. Despite these changes in neurosurgical training culture, the technique remains important for assisting the small numbers of individuals who present with extreme pathological challenges.

hfEC–IC has been performed since 1953 when Conley, an Ear Nose and throat surgeon used a Saphenous vein graft (SVG) to bypass the cervical internal carotid artery to aid resection of a tumour [6]. Whilst Yasargil *et al.* in 1967 reported on surgical techniques of revascularization in dogs, it was Lougheed *et al.* in 1971 who reported the first a successful "high flow" common carotid artery-to-intracranial carotid SVG bypass for athero-occlusive extracranial carotid disease [18, 38]. However, it was not until 1986 that a sizable clinical series emerged (with surgical technique and outcome) with 77 patients undergoing high flow was reported by Sundt [31]. They reported on successfully applying the technique for SVG bypasses into the M2 segment of the MCA and the P2 segment of the PCA.

The indications for a hfEC–IC can broadly be categorized into those required for carotid sacrifice to aid the complete resection of a neoplastic lesion at the skull base or high cervical region, and those required for cerebrovascular pathologies [28, 37] (see Table 1). The number of patients in which hfEC–IC is indicated remains small (Table 2). Indeed, over a cumulative period of 55 years only 460 hfEC–IC bypasses were reported world wide. Moreover, with improvements in stent technology and use of stereotactic radiosurgery, the potential need for hfEC–IC may decline although there is little evidence of this occurring to date [26].

Table 1. *Indications for cerebral revascularisation (tia's-transient ischaemic attacks)*

Tumours	A wide range of benign and malignant tumours of the skull base and head and neck have been treated with radical excision and bypass. Decision to bypass is made on tumour type, tumour location, tumour growth dynamics, extent of invasion and respectability of tumour. Bypass is rarely performed as a palliative procedure although in cases with a high incidence of complications arising from carotid invasion and destruction bypass has been performed.
Trauma	
Cerebrovascular diseases	
Cerebral ischaemia	Complete occlusion of the carotid with associated ''haemodynamic'' tia's from misery perfusion.
Aneurysms	Giant aneurysms • that are inaccessible (cavernous sinus aneurysms) • when prolonged temporary clipping during aneurysm surgery is anticipated • in those with in whom surgical or endovascular treatment is not possible because of; large intranidal thrombus, wide neck, calcified neck. • Dissecting aneurysms, fusiform aneurysms, or aneurysms with branches coming of the neck may also require consideration of bypass. • Bypass is also considered when a patient has bilateral giant aneurysms and when bilateral carotid sacrifice may be contemplated.

Patient selection is complex since there is no absolute indications for hfEC–IC; decisions are made on a case by case basis with the involvement of a multi-disciplinary team, the expertise and opinions of which may vary between institutions, and indeed within institutions as a function of time taking into account the pathology, physiological age of the patient, and the skill and availability of the surgical team, and access to other options.

One of the most robust indications for hfEC–IC is in the treatment of giant aneurysms. Giant aneurysms comprise 3–5% of all intracranial aneurysms [1]. The majority present with symptoms associated with mass effect, usually visual failure, cranial nerve palsies, seizures or hemipariesis [1, 7]. Drake reported that 35% of patients present with a subarachnoid haemorrhage, and some patients will have symptoms of transient ischaemic attacks from aneurysm associated thromboembolic disease [7].

Table 2. *Summary of outcomes reported by surgical teams performing EC–IC bypass*

Study	Study period	Patient no.	Indication	Bypass type	Graft patency	Complications
Regli *et al.* [26]	1979–1992	202	Aneurysm (37%), Carotid occlusive disease (63%)	High flow (SVG) ICA-ICA ICA/ECA/CCA/M2 ICA/ECA/CCA-P2	86% patency at 1 year; 82% at 5 years and 73% at 13 years	15% overall mortality from graft related occlusion causing infarction.
Hacein-Bey *et al.* [10]	1992–1997	9	ICA aneurysms	High flow and low flow (SVG and STA) ECA-M2	89% patency	11% neurological morbidity
Houkin *et al.* [13]	1989–1998	43	ICA anerysms	High flow (radial artery) ECA-M2	95%	4% ischemic complications
Morgan *et al.* [22]	1990–2001	55	Aneurysm (22%), Carotid occlusive disease (28%); neoplastic (30%)	High flow (SVG) ECA-supraclinoid ICA	93%	25% post operative deficits 7% mortality
Jafar *et al.* [14]	1990–1999	30	ICA aneurysms	High flow (SVG) ECA/CCA-MCA (84%) ECA/CCA-ICA(10%)	93%	3% Ischemic complications 3% Mortality
Van-Doormaal *et al.* [35]	1999–2004	34	Giant ICA aneurysms (with and without SAH)	High flow (SVG) ECA-ICA	100% (17% revision rate)	6% Mortality 12% Ischemic complications 3% technical failures
Mohit *et al.* [21]	1998–2005	101	Not specified	High flow (77%) 50% radial grafts; 50% SVG	99%	14% Ischemic complications 4% permanent neurological morbidity; 3% mortality
Kocaeli *et al.* [15]	2003–2007	13	Giant aneurysms (76%)	High flow radial graft ECA-M2 70%	100%	23% Ischemic complications
Kirkpatrick *et al.* (unpublished)	2005–2007	8	Giant aneurysms (100%)	High flow (SVG) ECA-M2	100% (1 graft revision)	12% anticoagulation related complications 12% graft complications (aneurysm)

SVG Saphenous vein graft; *ICA* internal carotid artery; *CCA* common carotid artery; *ECA* external carotid artery; *ICA* internal carotid artery; *M2* middle cerebral artery; *P2* posterior cerebral artery.

The natural history of giant aneurysms is universally poor. Drake reported a mortality of 68% at 2 years and 80% mortality at 5 years in his series of giant aneurysms treated conservatively [3, 7]. Therefore, a conservative strategy would not be appropriate in the majority of cases, particularly in the younger age groups. Direct surgical treatment of giant aneurysms by means of clipping and/or reconstruction is not possible in up to 50% of patients with anterior circulation aneurysms, and in 70% of patients harbouring posterior circulation abnormalities [8]. Whilst the advent of endovascular therapies has increased the number of such aneurysms amenable to treatment, this technique is also limited in the majority of cases [5]. The success of coiling of a giant aneurysm is dictated by the aneurysm's geometry including neck size and the presence of intra-luminal thrombus. For endovascularly treated aneurysms, there remains a high rate of recanalisation and rerupture even in tightly packed aneurysms. Increasingly with the advances in endovascular techniques, with the use of stents (covered and uncovered) and balloon remodelling to help to keep loops of coils inside the lumen, more aneurysms are amenable to treatment, although this is still fraught with a high rate of recurrence and exposes the patient to the risk of haemorrhage from an untreated lesions, as well as the potential complications from multiple endovascular procedures [5].

In the situation of an inability to surgically or endovascularly treat the aneurysm, because of the poor natural history, the default treatment is usually parent vessel occlusion: Hunterian ligation is a well accepted form of treatment for the treatment of giant aneurysms resulting in aneurysm obliteration in over 95% of patients with a giant aneurysms [8].

Whilst Hunterian ligation is widely accepted as a good management strategy of giant aneurysms, the indications for bypass remain controversial [17, 23]. Not all surgeons agree whether patients should undergo a balloon test occlusion first, with bypass being offered to only those that do not tolerate the trial occlusion [17, 23]. Those advocating a non selective revascularization strategy have argued that the results of bypass are better than the risks of balloon occlusion, that significant ischemia results with parent vessel occlusion without bypass, and that parent vessel sacrifice without bypass leads to an increased risk of aneurysm formation [17].

History reveals that surgical carotid occlusion for the treatment of an aneurysm results in cerebral infarction in upto 40% of patients, even if parent vessel occlusion is graded suggesting that a high proportion of patients cannot tolerate direct carotid occlusion [25]. Because of this high risk of stroke a number of techniques have been developed to ascertain the feasibility of parent vessel sacrifice. The contemporary method for evaluation of stroke risk from parent vessel occlusion is a test balloon occlusion test. This is a test which involves a 20–30 min occlusion of the parent vessel by a deflatable balloon, carried out under radiological guidance, endovascularly, in awake patients that

are clinically monitored. Adjuncts to clinical testing to increase the specificity and sensitivity of cerebrovascular reserve and stroke risk during test balloon occlusion have included measurement of carotid stump pressure, transcranial doppler of MCA flow velocities, SSEP monitoring, Xenon CT and SPECT imaging of cerebral blood flow [2, 4, 19, 29].

The overall complication rate following a test balloon occlusion is reported to be between 0–8% [20]. In the largest series published on the complications of balloon test occlusion (without deployment) the reported overall adverse incident rate was 3.2% [20]. This included 8 patients (1.6%) who developed were asymptomatic, either from a dissection, carotid pseudoaneurysm, or an embolus [20]. Transient neurological deficits were reported in 1.6%, and the overall permanent neurological deficit rate was 0.4%. The complications essentially represent those reported for diagnostic cerebral angiography which all patients undergoing evaluation for giant aneurysm would have to have and therefore does not constitute an additional risk [34].

The risks of cerebral ischaemia or infraction after internal carotid sacrifice after patients have clinically tolerated balloon occlusion are a different proposition. In this group of patients the permanent neurological morbidity rate is reportedly 1.5–4.8% whilst 10–12% of patients experience continuing transient ischemic attacks [9, 16, 30, 32]. It has also been suggested that cerebral ischaemia may not be apparent early, and the risk of delayed ischemia occurring has also been quoted at a rate of 1.4% per year [27]. However most of this risk is observed in the first year of carotid ligation, and it remains unclear whether these risks are from spasm related ischemia or a result of thrombosis and embolisation from the aneurysm, as both are a cause cerebral ischemia in this group of patients [16, 27, 36].

In reality of those patients that have clinically passed a balloon occlusion, only about 10% of patients have problems with delayed cerebral ischemia [4]. Most of this is not acute ischaemia, but that akin to 'misery perfusion' as seen with occlusive carotid disease. Given this, we advocate a selective revascularisation approach, reserving a bypass for those patients that have failed to tolerate 20 min a trial balloon occlusion based on clinical features, as well as angiographic findings of absence of synchronous venous filling and >50% drop in the middle cerebral artery blood flow velocities. All our patients are given acetazolamide pre procedure so that the balloon occlusion is performed in patients with the neurovascular bed 'under stress'. Patients that have developed cerebral ischemia (invariably presenting with transient ischaemic symptoms rather than acute stroke) in a delayed fashion can be re evaluated, undergo cerebral blood flow imaging pre and post acetazolamide, and if necessary hfEC–IC. Further, it is important to appreciate that low blood flow states are dynamic, and may improve with time with the increase in leptomeneingeal collateralization. We emphasize again that decisions need to be made

in an individualized manner, because what is appropriate for a patient with for example an unruptured aneurysm may not be appropriate for a patients that present with a subarachnoid haemorrhage.

The other major concern of surgeons favouring a universal revascularization strategy is the formation of denovo aneurysm as a result of the change in flow dynamics (mainly increased flow in the contralateral carotid) after balloon occlusion [17]. These aneurysms have been reported in the territory of the occluded vessel, and also remote from it, and have been reported in up-to 10% of patients [17]. Whilst undoubtedly the flow dynamics of the cerebrovasculature is changed following parent vessel occlusion, most of the literature on denovo aneurysm formation is from the 1960s and early 1970s and may represent missed aneurysms at the time of initial angiography from poorer quality examinations. Further there is no evidence to suggest that an interposition graft is not associated with denovo aneurysm formations because the long term results are not yet available. There are certainly case reports that suggest that hfEC–IC can alter cerebral haemodynamics enough to cause rupture of an unprotected aneurysm [12, 24].

To summarise, we reserve consideration of an hfEC–IC bypass to those patient who have major vascular pathology who attract a poor natural history, and who would otherwise be expected to survive for some years. They all must have failed a test balloon occlusion test judged on clinical and transcranial Doppler and angiographic criteria. Those who have initially tolerated carotid occlusion but then have developed ischaemic symptoms, cerebral hypoperfusion syndrome is confirmed with appropriate cerebral blood flow imaging.

Surgical technique (see Table 3)

The key theme to performing a hfEC–IC is the introduction of multiple quality control measures testing each end point of each part of the procedure (see Table 3 for surgical check list used for surgery). The consequence of failure at any point of surgery is at best graft failure, at worst a life threatening complication. Unless these quality insurances are meet, it is our view the patient would be best served avoiding such a procedure.

The operation usually lasts around 4–5 hours and hence is always performed under full general anaesthesia with urinary catheterisation and a central line to ensure optimal fluid management. Rheological agents, such as mannitol, are avoided until the graft is established (vide infra). Sites of proposed incision are discussed with the anaesthetist before induction of anaesthesia to ensure that the necessary central and arterial line placement is not at the site of proposed incisions. All patients receive antibiotic prophylaxis at induction.

All patients undergoing bypass for giant aneurysms are commenced on Aspirin 300 mg a day to minimize the risk of thromboembolic complications and encourage graft survival in the early phase.

Table 3. *Check list of measures considered to optimize surgical success and graft survival*

Cranial exposure	• Meticulous attention to bleeding and appropriate haemostasis • Appropriate, exposure and mobilization of recipient vessel to provide room for formation of anastamosis with temporary clips in situ • Absence of perforating vessels on recipient vessel • Appropriate caliber of vessel to receive SVG
Cervical exposure	• Meticulous attention to haemostasis • Adequate exposure of ECA • Oval arteriotomy in ECA when required
Pre auricular tunnel	• Create early to allow for the subcutaneous ooze to settle • Generous subcutaneous dissection to ensure no compression of graft
Graft extraction	• Adequate length of graft (20–25 cm) • Ligation of side vessels flush with the graft • Graft left in situ until required
Graft preparation	• Valvulotomy and pressure distention to ensure flow in both directions • Removal of adventia at both ends of the graft • Ensure no large graft/recipient vessel mismatch
Anastamosis	• Check haemostasis • Arteriotomy to match size of SVG • Secure heel and apex of graft first • Ensure subsequent sutures are placed starting as close to the apex and heel of the graft • Ensure back wall not compromised with the sutures • Graft allowed to back fill with blood before tunneling • Avoidance of redundant intracranial graft to prevent kinking of graft
Pre closure assessment of vasculature	• Doppler assessment of the MCA with graft occluded • Back bleeding through side port with graft occluded just distal to ECA • Back bleeding through side port with graft occluded proximal to MCA • Closure of side port • Doppler assement pre closure of whole length of graft • Break for 30 min before reassessment of graft
Closure	• Attention to closure to ensure no graft compression from replaced bone flap, muscle closure, skin closure
Post operative care	• Maintain normovolaemia, normotension • Avoid inadvertent external graft compression from face masks etc. • Regular hand held Doppler surveillance of graft • Post operative angiography to ensure graft patency prior to parent vessel occlusion

We have a long history of intraoperative monitoring, but for this procedure no monitoring is routinely used. We feel that the ischemic insult caused by bypass on to the M2 branch of the middle cerebral is minimal, and generally well tolerated. In this setting, we feel that monitoring with somatosensory evoked potentials as advocated by some authors may lead to pressure to rush the anastamosis which is a critical part of the procedure. We accept however that when the bypass is performed onto a more proximal vessel, monitoring would be beneficial particularly to guide the need for 'neuroprotective' adjuncts such as burst suppression.

The head is fixed and held in a Mayfield clamp, and the patient is placed supine with the head turned 90° away from the side of surgery. A sandbag is placed under the contralateral shoulder to aid rotation of the head, and the head of the operating table is elevated by 30°. A large sandbag is also placed underneath the ipsilateral thigh to aid slight external rotation of the lower limb that facilitates access the Saphenous vein in the leg. As with all neurosurgical procedures, attention to position, and pressure points is routine.

The procedure is lengthy, technically challenging, and requires a meticulous approach at all times of the surgery. Because of this and to minimise the effects of tiredness, we normally have two senior surgeons involved in the surgery. Typically, surgeon A would perform the craniotomy and exposure of vessels in head (∼45–60 min) and in the neck (cervical exposure 30 min). Whilst surgeon A takes a break surgeon B proceeds to harvest and prepare the graft (∼90 min). Surgeon A rested then performs the proximal and distal anastamosis which are the most challenging and tiring part of the procedure.

Cranial exposure

Through a standard curved hairline incision, a Pterional craniotomy is fashioned. Following removal of the sphenoid wing, the dura is opened based on the sphenoid wing. The dura is also tacked back over linteen strips at the edge of the wound to minimize ooze from the wound contaminating the field adjacent to the anastamosis. Attention to haemostasis is critical at every step of the procedure from skin to dural opening because of the need to anticoagulate the patient during vessel cross clamping. Dural hitch sutures are not used routinely, as in our experience they do not serve a purpose.

The Sylvian fissure is split widely to identify an M2 branch of the Middle cerebral artery (MCA). The M1 branch is not generally used because of the presence of the perforating arteries. Mohit *et al.* have suggested that in cases where the M1 segment is short, there may be perforating branch of the M2 segment which would make these vessels unsuitable [21]. In this situation he recommended that the communicating segment of the ICA is used as the site of the distal anastamosis. However, this has not been our experience and we have yet to be unable to anastamose to one of the proximal M2 segments.

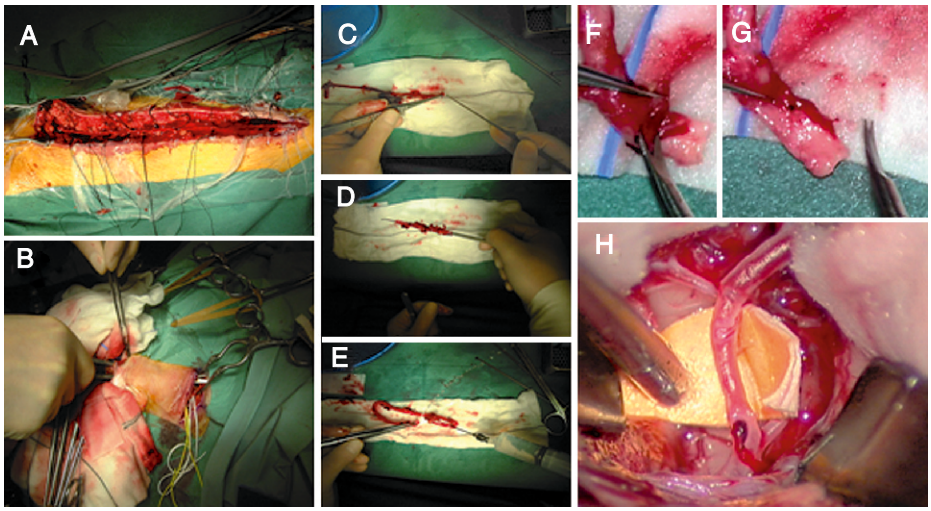

Fig. 1. (A) Graft exposure demonstrating the length of dissection and the number of side branches that need to be ligated. (B) Creation of pre auricular tunnel (C–E) preparation of the graft with destruction of the valves with a disc dissector to allow for flow reversal, and pressure distention to check there are no leaks and that there are no patent valves before implantation. (F, G) Removal of graft adventitia (H) M2 recipient vessel mobilized and prepared for graft implantation

The size of the M2 segment is important and we tend to target the most generous branch. Once the Sylvian fissure is split, and the appropriate M2 branch is identified, the vessel is freed of arachnoid adhesions allowing mobility of the segment. A piece of coloured card (usually derived from the packaging of the 10/0 nylon suture) is softened in saline, shaped and sized, and inserted underneath the site of proposed anastamosis to provide contrast to allow for better visualization of the vessel wall during the anastamosis (Fig. 1). The wound is then filled with warm saline.

Cervical exposure

A transverse skin crease incision at the level of the hyoid is made to expose the Carotid bifurcation. The incision is transverse mainly for cosmetic reasons, but can be extended longtitudinally in cases where the carotid bifurcation is difficult to expose. The Sternomastoid muscle is mobilized laterally, to expose the deep cervical fascia and the Carotid sheath both of which need to be opened to expose the Carotid artery. We usually plan for an end to side anastamosis between the graft and external carotid artery (ECA). This requires exposure of the ECA for about 2 cm beyond the bifurcation so that there is enough room to create the bypass after the application of temporary vascular clamps. Avoiding the internal carotid artery (ICA) is clearly important in the context

of intracranial flow arrest during anastamosis, which takes approximately 30–45 min. These patients have already failed a balloon occlusion test, and therefore, this length of time would not be tolerated. If the ICA has to be involved due to anatomical variations and an inadequate ECA, due consideration to a carotid shunt is necessary.

Saphenous vein exposure (Fig. 1)

The Saphenous vein consistently runs from anteriomedial to the medial Malleolus where it can invariably be seen or palpated, to the knee where it lies a hands width posteriomedial to the patella. From this point it passes upwards on the medial aspect of the thigh to join the femoral vein in the groin. We harvest the saphenous vein from the ankle to the lower thigh. Pre operatively it is important to check that the patient does not have varicosities of the Saphenous vein, and they have not had any previous surgery that may have compromised the Saphenous vein. We also routinely examine and mark the course of the Saphenous (at the ankle and lower leg) vein pre-operatively with the patient in the standing position. At the time of surgery, the vein is identified first at the ankle before the dissection proceeds toward the knee. Approximately 20–25 cm of vein is exposed and mobilized. During the mobilization procedure all the side branches are ligated with a 4.0 silk suture or secured with titanium haemoclips (Fig. 1). It is important that the ligation is flush with the vessel wall without compromising the lumen. We purposefully do not ligate flush one or two of the larger side branches. These are left so that the side branches can be reopened after the completion of the anastamosis so that flow in both directions of the bypass checked, and air can be vented. They also act as portals to allow graft exploration with various probes if a technical problem has arisen and the graft is found not be conducting appropriately.

Once the graft is prepared, it is left in situ until it is required. Thus the cranial and cervical vessels have been fully exposed and prepared, and haemostasis ensured. At this point it is ligated at both ends and removed. We flush the graft with heparinized saline, and clean the graft of the redundant connective tissue and adventitia at both ends of the graft (Fig. 1). The removal of the adventitia at the proposed cranial end of the graft is cleaned for approximately 2 cm (Fig. 1). This is to minimize the sticking of the sutures to the side walls of the vessel during the time of the anastamosis. The valves in the graft are broken down by passing a series of disc dissectors up and down the graft. Multiple passes of the dissector, oriented in slightly different radial positions, ensures that each valve is sliced in multiple directions to ensure bi-directional and seamless flow. The patency is confirmed by flushing with heparinized saline in both directions. Finally, a probe is passed down the lumen of the graft which is scrolled up along the shaft to allow some degree of mechanical dilation. We cannot stress enough the importance of this manoeuvre, since

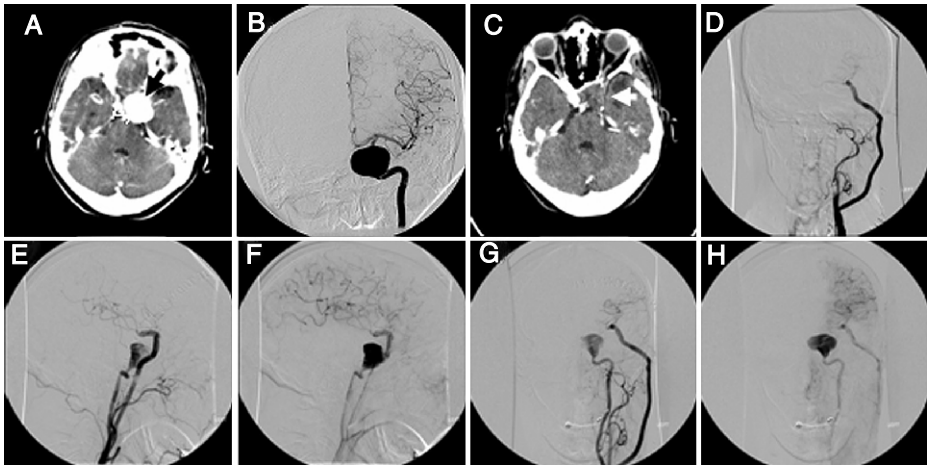

Fig. 2. These are the images of a 56 year old lady who presented with a cavernous sinus syndrome on the left side. Her contrast enhanced CT scan (A: arrow demarcated aneurysm) and cerebral angiogram (B) revealed a left sided intracavernous aneurysm which was treated with ECA-M2 bypass followed by balloon occlusion 4 days following surgery. The flow into the aneurysm stopped immediately following the balloon occlusion (D), and the aneurysm was noted to remain obliterated on the 3 month contrast enhanced CT scan (C). These images also demonstrate balanced flow in the graft and the internal carotid on a common carotid injection (E–H). This argues against concerns expressed by a number of surgeons who maintain that early/immediate closure of the parent vessel is necessary to encourage flow in the graft

failure of the graft can be a consequence of inadequate graft preparation. Compensation for the valves by reversing the direction of the graft (ankle end for proximal anastamosis) is not something we recommend since the flow dynamics favour a tapering graft which narrows towards the distal anastamosis (Fig. 2). This promotes an acceleration of flow, a factor which may bear importance in maintaining the graft when no pressure gradient exists (i.e. before balloon occlusion of the parent ICA some days later). We also believe that a valved graft will not allow bi-directional flow which may encourage thrombosis within the pockets (flow shadows) of each valve. The smaller ankle end of the graft is also more suitably sized for anastamosis to the M2 branches and vice versa.

Once devalved and dilated, the cranial (ankle) end of the graft is cut obliquely, and fishmouthed in preparation for the distal (cranial) anastamosis (Fig. 1).

Pre auricular tunnel

A pair of Roberts forceps is inserted proximal to distal into the pre-auricular tunnel and the lower end of the graft is grasped before the temporary clip is

removed. The deflated graft is pulled through with enough tension to ensure that there is no redundant intracranial loop, and that there is no twist or kink in the graft. As a quality check the graft patency can be ensured after this part of the procedure by releasing the distal graft clip and allowing back flow towards the cervical incision. Once this has been observed, the graft is again refilled with heparinised saline as for above (Fig. 1).

Anastamoses

Just prior to creation of the anastamosis, the patient is given a 3000 unit bolus of Heparin intravenously. We do not routinely perform this procedure under burst suppression or hypothermic conditions, although we do advocate that the blood pressure is maintained at a slightly elevated level (as compared to pre-operative state) to optimize flow though the collateral circulation.

Distal anastamosis (Fig. 3)

We perform the distal anastamosis first allowing maximal mobility of the graft which can be flipped over to allow for better visualization of the posterior wall of the vessel. Following application of proximal and distal temporary clips low pressure clips oval arteriotomy of approximately 5 mm in length (to match the size of the opening of the harvested saphenous vein) in the recipient vessel is created. Sutures at the apex and the heel of the graft are placed to stabilize the

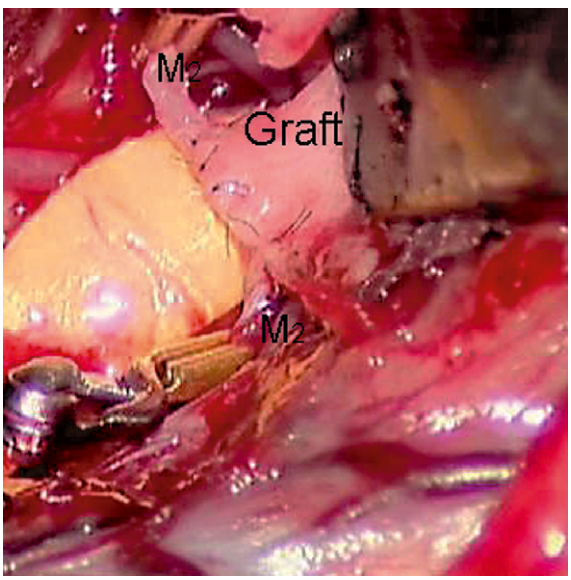

Fig. 3. Intracranial anastamosis

graft against the recipient vessel. The intracranial anastamosis is performed with interrupted 10-0 nylon sutures starting at a point closest to the heel or apex of the graft. The technique preferred for sitting the interrupted sutures is to lay flat all sutures for one side cut to a similar length. Once in place they are tied in sequence starting at the end which most recently received the suture since these ends will overlap earlier sutures. On completion of each knot the ends are trimmed to reduce clutter.

Once one side is complete, the graft is flipped over to access the remaining side. Improved exposure and access of the unsutured side can often be achieved by holding the graft in place by means of additional low pressure clips, or even a fixed retractor blade (Fig. 2). Lumen patency is checked whilst closing the posterior wall to ensure that the lumen has not been compromised by inadvertent stitch placement. The use of a blunt hook inserted into the M2 vessel (both directions) is carried out on a regular basis.

The clamp time to allow for the creation of the anastamosis should ideally be no more than 30 min. However, given that the donor vessel is an M2 branch we believe that collateral flow at this level to be reasonable as assessed by the back flow pressures usually seen. Longer clamp times are therefore likely to be tolerated without too much concern.

After the anastamosis is complete, the temporary clips are removed, and the graft is allowed to 'back bleed' and fill up before a temporary clip is placed at the midpoint of the graft. This implies patency of the distal anastamosis. The site of the anastamosis is also checked to ensure there is no leak that requires a further suture. The site at which leaks are most commonly noted are in the region of the apex or heel of the graft, emphasizing the importance of placing the first sutures as close to the anchoring sutures as possible. Small leakages are tolerated and surgical wrapped around the graft to encourage spontaneous haemostasis. However, a significant pulsatile haemorrhage will usually need a further suture which is best placed with the graft and anastamotic site inflated to prevent inadvertent catching of the opposite vascular walls.

Back bleeding of the graft is important also to perfuse the graft endothelium to minimise the effects of ischaemia. After this, and once reasonable haemostasis is secured, heparinised saline is introduced into the free end of the graft and irrigation provided whilst an aneurysm temporary clip is applied close to the anastamosis site. The rest of the procedure is carried out with the graft full of heparinised saline, although if there are any delays with the proximal anastamosis, the graft is back bleed again to perfuse to minimise the effects of endothelial ischaemia.

External Carotid anastamosis

The external carotid anastamosis is performed with interrupted (9.0 nylon) suture in an end to side fashion on the ECA. Artery slings can be manipulated

to allow the donor vessel to be presented more favourably into the wound since the depth of the vessels can present difficulties in carrying out the anastamosis. After application of temporary clips on the proximal and distal ECA, an oval arteriotomy is created. Direct vision into the lumen of the external carotid is an essential part of this section of the operation since intimal flaps can be readily missed. A simple slit incision, in our experience, is insufficient and will often seal resulting in early graft failure. The SVG is cut to size (to minimize excessive kinks and redundant loops) and fish-mouthed as already described. The extracranial anastamosis also proceeds in the same fashion as the described for the intracranial anastamosis with the same check points applicable.

Following completion of the bypass, the temporary clip on the distal graft is released to re-confirm back filling and vent air. If haemostasis is reasonable the external carotid clamps are removed to establish anterograde flow in the graft. Any major leaks can be addressed with interrupted 9/0 sutures.

The availability of side venting ports are invaluable in quality assurance assessing competency of flow and direction (it is not impossible for the graft to cause reverse flow if the proximal anastamosis is compromised). A hand held intraoperative Doppler probe is also essential at this point to assure the surgeon that antegrade flow is present within the graft, and flow is continuous in both systole and diastole.

Though a combination of application of temporary clips proximal or distal to the venting port, and insonation with a handheld Doppler probe, flow and patency of various portions of the graft can be ascertained. Once the operator is satisfied that good quality anterograde flow has been achieved, the patient is given 200 ml of 20% mannitol as a rheological agent to increase graft and cerebral blood flow, and as an anti-oxidant agent to improve the health of the graft which may have been rendered ischaemic during the non-flow stage of the surgery.

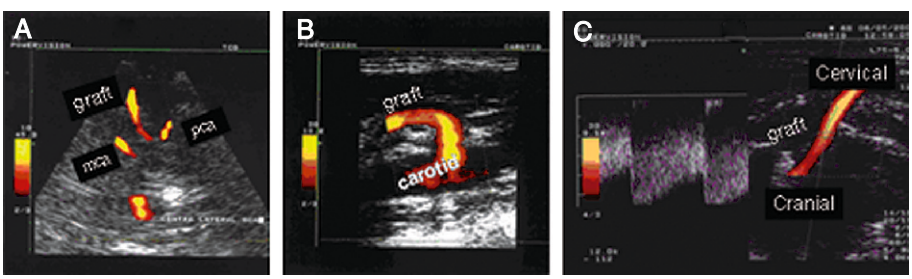

Fig. 4. These images demonstrate the application of transcranial colour doppler (TCCD) for graft surveillance. (A, B) Demonstrate that the proximal (B) and distal (A) anastamoses are patent, whilst (C) shows that flow is in an antegrade manner; i.e from the carotid to the middle cerebral as measured at the midpoint of the graft

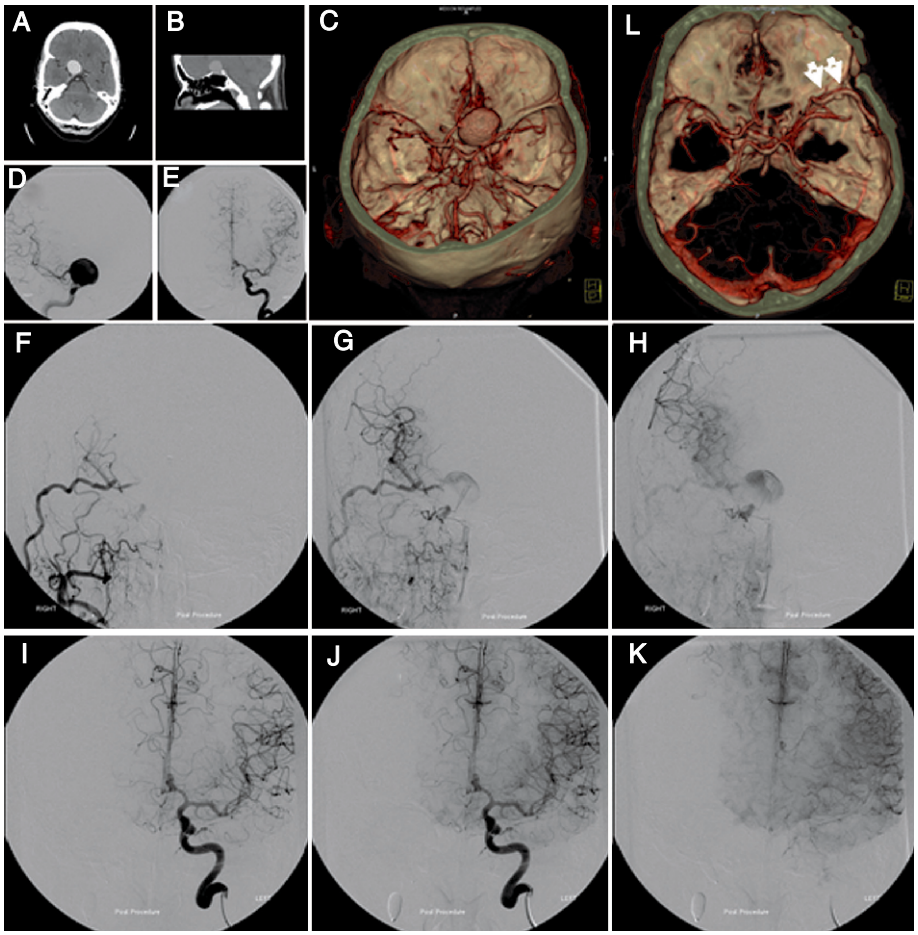

Fig. 5. These images demonstrate a typical case from our series of hfEC–IC bypass for giant aneurysms. These images of a 60 year old patient who presented with visual deterioration in the right eye. Her CT head scan (A, B) revealed a right paraclinoid mass which was demonstrated to be a giant carotico-opthalmic aneurysm on a CT angiogram (C). She underwent cerebral angiography which demonstrated good anterior circulation crossflow, but she failed a test balloon occlusion (D, E). She therefore underwent an ECA to M2 bypass, and had a delayed (2 days post bypass) occlusion of her carotid artery endovascularly. The post balloon angiogram demonstrated filling of the right anterior cerebral from the left side as noted preoperatively, and the right middle cerebral territory supplied by the graft (F, G; right common carotid injection; I–K left carotid injection). Following the balloon occlusion, the aneurysm was still noted to be filling (F, G). The patient was reviewed 4 months later when she remained well, the graft (arrows) was patent, and the aneurysm was no longer filling (L). She had no objective change in her visual symptoms

We then recommend observing the graft for a full 30 min and re-checking the end-points of the operation before closing.

Closure and post operative care

Once the patency of the vasculature has been confirmed, the side arm of the graft is closed using a silk suture or haemoclip. Closure of all the wounds proceeds in a layered fashion with a repeat attention paid to haemostasis prior to closure because the heparin is not reversed. Attention to closure around the graft is also critical to ensure that the graft is not compromised by replacement of the bone flap, closure of temporalis, or poorly placed sutures in the head and neck. Post operatively external compressions from facemask elastic to securing for an endotracheal tube if necessary also need to be avoided. The patient is managed on a critical care unit with strict instructions to maintain euvolaemia, and normotension. The graft is monitored with a hand held Doppler.

Long term surveillance is performed with a transcranial Doppler ultrasound which assesses flow, direction of flow, and allows visualisation of the entire bypass quickly, and non invasively in the clinic setting (Fig. 4).

Using this technique we have performed 9 hfEC–IC bypass grafts over the last 2 years as part of the treatment for giant intracranial aneurysms. Our median follow-up is currently 12 months. Although, we have had one early graft failure that required revision all grafts were patent and revascularising the hemisphere at the time of balloon occlusion (Fig. 5). We have experienced no ischemic complications resulting from the surgery. One patient in this series developed an anticoagulant related complication (subdural haematoma). This was managed conservatively and there were no resultant long term complications. One patient developed a graft site aneurysm in the preauricular region. This was at the site of a side vessel that was not appropriately ligated flush with the graft vessel and required surgical excision and repair of the graft site.

Discussion

Comparison of outcomes

The results of the experience of a selection of surgeons performing hfEC–IC are summarized in Table 2. Most of these series represents the overall experience of the respective surgical teams and do not stratify results by pathology. This makes overall outcome in patients undergoing hfEC–IC difficult to interpret because of the wide range of pathologies for which hfEC–IC is performed. Even for results published for giant aneurysms, the heterogeneity introduced by whether patients have presented with a subarachnoid haemorrhage or not, makes interpretation of results difficult. Overall outcomes in these situations tend to be driven by the underlying disease process and cannot

entirely be related to surgical morbidity associated with the creation of bypass. These problems in assessing outcome overall is a result of the low number of patients that require bypass.

Outcome however can be assessed on the basis of surgical factors such as graft patency and surgical complications. Graft patency rates are high, and average 93%, and most surgical series agree that early graft failures can be related to intra-operative problems and are due to technical problems [13, 15, 21]. This emphasizes the importance of surgical technique and having in place quality control measures for each section of the operative procedure as emphasised in this article.

Choosing the type of graft

In general, when major parent vessel occlusion is planned, "low flow" vessels (which typically support flows of 25–30 ml/min) such as the superficial temporal or the occipital artery are not normally sufficient to revascularise a whole hemisphere. In this situation, "higher flow" vessels such as the radial artery (supports flow of between 50 and 150 ml/min) or saphenous vein (100–200 ml/min) are necessary. In addition to flow, graft selection depends on, availability of the graft, size of the recipient vessels, as well as the preference of the surgical team. Both saphenous and radial artery grafts have practical advantages and disadvantages. Radial artery grafts are more difficult to harvest. They are notoriously prone to severe spasm leading to shortening of the harvested vessel. These problems with graft shortening due to spasm can be overcome by the use of judicious application of pressure distention and by soaking in Papaverine [21]. The advantages of working with a radial artery grafts is that there is less of a size mismatch between the graft and the recipient vessel, and therefore there is less turbulent flow at the level of the anastamosis. These features also reportedly make the distal anastamosis easier to perform [13, 15, 21].

The argument for the use of SVG is that it is easier to harvest, supports greater flow, and that grafts are not prone to significant spasm. This is balanced against the disadvantages of the size mismatch, and the presence of a fragile endothelium which contribute in making the distal anastamosis more difficult to perform.

We prefer to use a SVG because of ease of harvesting, and because of ease of handling due to lack of spasm. Our experience of radial artery graft is that it causes significant forearm morbidity. Further getting the vessel back to a suitable length for the bypass requires considerable pressure distension and Papaverine. We are however mindful of the mismatch in the size between the graft and proximal receiving vessel but have had no problems that have required changing the site of anastamosis or graft to date.

Long term patency of grafts

Long term patency results are unfortunately limited, although a series from the Mayo clinic using Saphenous grafts with follow-up for 13 years, has suggested a 1–1.5% attrition rate for SVG grafts [26]. In comparing graft survival according to type of graft used, some have argued based on the cardiovascular literature, and experimental literature (porcine venous grafts were more prone to accumulation of low density lipoprotein deposits, and developed accelerated atherosclerosis as compared to arterial grafts) suggests that radial (indeed arterial) grafts may be better, but this is not substantiated in the neurosurgical literature [15]. In the long term, it is unclear as to how long a graft needs to last for, with the logical assumption being that the graft would be required for the life of the patient. One of our cases who having failed a balloon occlusion underwent an hfEC–IC graft for treatment of a giant ophthalmic aneurysm. Four months later, she developed a pre-auricular graft site aneurysm which needed resection and repair with an interposition graft. At the time of surgery, the back pressure in the distal portion of the graft was very high suggesting that the graft may not be required as a result of substantial leptomeningeal collateral development.

Anecdote aside, late graft failure remains an important consideration. The cause of this is thought to be because of a combination of 'arterialisation' of the graft with resultant intimal and smooth muscle hypertrophy, and resultant or coincident accelerated atherosclerosis [26, 15]. It is critical therefore, that post operative care includes medical and life-style strategies to optimize cardiovascular health. We routinely ask that the patient refrains from smoking, and that they submit to annual medical surveillance for hypertension and hypercholestrolaemia.

Ischaemic complications

One of the great concerns of hfEC–IC is the potential risk of cerebral infarction as a result of clamp time on the distal (intracerebral vasculature) required to perform the distal anastamosis. This clamp time varies according to surgical expertise and familiarity, and is estimated at between 20 and 50 min, and depends on the site of the anastamosis. The risk of cerebral ischemia intuitively is increased when the distal anastamosis is performed on the ICA and may be reflected in the high risk of post operative neurological deficits reported by Morgan *et al.* [22] (14%) and Lawton *et al.* [17] (16%) who performed bypass onto the supraclinoid ICA [17, 22]. This is contrast to those contemporary series including our own that have reported an ischaemia related neurological morbidity of between 0 and 6% with a hfEC–IC onto the middle cerebral branches [14, 21]. That major branch occlusion results in increased ischemic complications is further suggested by the reluctance to bypass onto the M1 because the territory supplied by the M1 perforating arteries is intolerant of

ischemic insults [21]. Because of this risk of infarction, we constantly perform our distal bypass onto the M2 to good effect.

More recently, the excimer lazer assisted technique (ELANA) has been pioneered to allow an anastamosis to be performed without parent vessel occlusion [35, 33]. Whilst this technique is a significant aid to performing bypass, it still requires the technical skill and quality control measures necessary to perform bypass because the failure rate of the laser to create a suitable opening is high, and this may necessitate the use of conventional techniques. Initial results whilst encouraging they have not reported a reduced stroke risk as compared to series in which patients underwent bypass without the ELANA technique [14, 17, 21, 22, 35]. However, it has to be noted that the reports are on patients that have had bypass for giant aneurysms some of whom have presented with a subarachnoid haemorrhage.

Early graft occlusion is responsible for a significant proportion of cerebral ischemia related morbidity [35]. This again emphasizes that need for quality control through out the procedure, and mindful of this, a number of surgical teams have come to rely on intraoperative angiography as part of the quality control for the procedure [21]. Indeed this is thought to be one of the major reasons why some authors report graft patency rates of 99–100% [15, 21] compared to the series from Sundt *et al.* [31] that reported a graft patency rate of 83%. Intraoperative angiography is not widely available, and good graft patency rates can be achieved without intraoperative angiography using techniques as described above. We use a number of measure to check patency before the patient leaves the operating theatre that have been documented above. We feel that the quality of the Doppler signal from the graft particularly hearing flow in both systole and diastole combined with the other measure including rechecking the graft 20–30 min after creation of the anastamosis is a robust enough quality control measure to ensure graft patency. More recently, with the advent of indocyanine green angiography technology, on table "angiography" to assess graft patency has become easier at centres that have this facility.

One of the other important factors with regard to morbidity associated with early graft failure however may be related to the timing of the parent vessel occlusion. The risks of occlusion if a graft fails with early/immediate parent vessel occlusion are high, and in this setting, we would agree that contemporary practice dictates that intraoperative or pre-parent vessel sacrifice angiography to demonstrate graft patency is mandatory. However, in most cases, immediate parent vessel occlusion is not necessary, although there are reports of early aneurysm rupture from change in flow dynamics in the intracranial circulation. Again decisions with regard to this have to be made on a case by case basis, mindful of potential complications, and the available quality control measures. We routinely perform delayed (2–4 days) cerebral angiography to assess the patency and quality of the graft before proceeding to balloon occlusion of the

parent vessel. There have also been concerns from some authors that early parent vessel occlusion is necessary to encourage flow the graft. This is not borne out by our experience and as illustrated in Fig. 2, balanced flow is achieved between the graft and the carotid using the technique described above.

Anticoagulation related morbidity

The final major concern with regard to bypass related morbidity the need to anticoagulate the patient during the procedure. One patient in our series developed an acute subdural post operatively. Lawton *et al.* reported that 5 out of 61 patients (8%) had a post operative extradural haematoma, and Hecin-Bey *et al.* (although in a smaller series) reported a anticoagulation complication rate of 33% (this included 2 femoral pseudoaneurysms) [10, 17]. As a result of these complications some authors have advocated routinely reversing the heparin given as part of surgery once the graft is established. In these series, the post operative problems resulting from a bleeding diathesis are significantly lower (0–3%) [14, 21]. Indeed, there are some surgical teams that do not systemically anticoagulate their patients, preferring to use copious amounts of heparinised saline during the operative procedure. The potential for thromboembolic complications in the graft in this setting are higher, and mandates the availability of appropriate quality control measures such as intraoperative angiography, and or intraoperative Doppler. We routinely do not reverse the anticoagulation because of the potential thrombotic complications. This approach necessitates meticulous attention to bleeding from the start of the operation. It is important to point out that most of the bleeding related complications reported in the literature occur remote from the anastamosis site emphasising the importance of haemostasis at each phase of the procedure.

Conclusion

hfEC–IC bypass to allow parent vessel occlusion is an important treatment for patients with giant intracerebral aneurysms. Surgery for hfEC–IC bypass is technically challenging. However, many authors have performed this surgery with good graft patency rates and low morbidity. We advocate performing this surgery in a stereo-typed and meticulous fashion with multiple quality control checks at each phase of the procedure.

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Decompression for Chiari type I-malformation (*with or without syringomyelia*) by extreme lateral foramen magnum opening and expansile duraplasty with arachnoid preservation: comparison with other technical modalities (Literature review)

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With 3 Figures

Contents

Abstract

Posterior craniocervical decompression is the procedure most currently used for treating Chiari I malformation (alone or in association with syringomyelia in the absence of hydrocephalus). We reviewed the various technical modalities reported in the literature. We present a personal series of 44 patients harboring Chiari type I malformation (CM-I) operated with a suboccipital craniectomy and a C1 (or C1/C2) laminectomy, plus an extreme lateral Foramen Magnum opening, a "Y" shaped dural incision with preservation of the arachnoid membrane, and an expansile duraplasty employing autogenous periosteum. Outcomes were analyzed with follow-up ranging from 1 to 10 years (4 years on average).

The presented technique was compared with the other surgical modalities reported in the literature. This comparative study shows that this type of craniocervical decompression achieved the best results with minimal complications and side-effects. Syringomyelia associated with CM-I must be treated by craniocervical decompression alone. Shunting no longer appears to be an appropriate method of treatment for syringomyelia.

Keywords: Chiari type I malformation; foramen magnum decompression; syringomyelia; cerebrospinal flow; posterior fossa surgery.

Introduction/Definition

First described by Hans Chiari (1851–1916) in 1891 [9] in Deutsche Medizinische Wochenschrift and entitled "concerning alterations in the cerebellum resulting from cerebral hydrocephalus", this entity came to be known as Chiari type I-malformation (CM-I) [5]. Nowadays, CM-I is described as caudal descent of the cerebellar tonsils through the foramen magnum into the spinal canal, at least 5 mm below the plane of the foramen magnum, without involving the brainstem. In 32% to 73% of patients, CM-I is associated with syringomyelia [20, 28, 37, 46, 68, 69]. More recently, the Chiari type 1.5-malformation has been described [65, 66]. Its essential difference with CM-I is that in addition to tonsillar ectopia, patients with Chiari type 1.5-malformation also exhibit caudal descent of the brainstem [65]. Management of this subtype is the same as for CM-I.

When progressive syrinx enlargement and/or other symptoms related to CM-I is/are noted, a posterior decompression of the cervico-occipital junction is commonly offered. The aim of the surgery is to halt the progression of neurological signs and symptoms of the condition [12]. Whilst some improvement in the patient's condition often results from the procedure, patients must be aware that this is not the principal goal. The aim of the procedure it to relieve the compression of the neural structures, and to re-establish cerebrospinal fluid (CSF) circulation within cisterna magna, as this appears to be the most logical means of counteracting pathophysiology of syringomyelia.

In adults, it is commonly during the third decade that CM-I is highlighted, after several years of headache, neck pain, arm weakness, numbness, spasticity, and dissociated sensory loss. Headaches are typically aggravated by Valsalva manoeuvres. It is now well established that this pathology is the result of a particularly small and shallow posterior cranial fossa, which itself is due to an underdeveloped occipital bone [43, 55, 59, 62, 71].

Furthermore, intracranial hypotension syndrome may be mistaken for a CM-I and has to be excluded. Imaging also evidence descent of cerebellar tonsils. Usually, it is characterized by an orthostatic headache [29, 38, 45, 49]. In addition to headache, patients may experience nausea, vomiting, neck pain, dizziness, horizontal diplopia, or radicular symptoms, all of which are orthostatic in nature. There is strong evidence indicating that most cases of intracranial hypotension result from a persistent CSF leak (after dural puncture, ventricular shunt and any time the dura matter is violated) [30]. The major abnormalities demonstrated on MRI studies are diffuse thickening of the pachymeninges with gadolinium enhancement, engorgement of venous sinuses, and downward displacement of the cerebellar tonsils [39]. Intracranial hypotension generally is considered to be a benign condition, and most cases resolve with conservative management [45].

Surgical treatment of CM-I can be applied by several technical modalities, some of which are controversial. A suboccipital craniectomy is universally accepted, but combining it with laminectomy, opening or leaving dura matter closed, opening or respecting arachnoid, lysing of the arachnoid, shrinking or resecting cerebellar tonsils, stenting the fourth ventricle, plugging the obex, performing a duraplasty and the optimal material for it, leaving the dura open, and the need for cranioplasty are still debated.

Generalities

Chiari type I-malformation pathophysiology

It is now accepted that CM-I results from either a mesodermal defect after the closure of the neural folds, which leads to the underdevelopment of the basichondrocranium which in turn results in disproportion between the container (skull) and the contents (neural elements), or to an overgrowth of the supratentorial component and consequent shallow posterior fossa. Too bulky for this hypoplasic posterior fossa, the cerebellar tonsils herniate through the foramen magnum [31, 35, 42, 77] obstructing the normal venting of CSF in and out of the craniocervical subarachnoid space, throughout the systolic time of cardiac cycle [13]. Chronic occipital and/or posterior cervical pain may be due to reflex irritation of the dura of the posterior fossa. Headaches associated with Valsalva and all maneuvers that increase intracranial blood volume, induce temporary intracranial hypertension resulting from

the trapped CSF by cerebellar tonsils impaction at the level of the Foramen Magnum.

Syringomyelia pathophysiology

Syringomyelia causes progressive myelopathy. Determination of the pathophysiological mechanisms underlying the progression of syringomyelia associated with the CM-I, should improve strategies to halt the progression of myelopathy. Despite many hypotheses, the pathophysiology of syringomyelia is still not well understood.

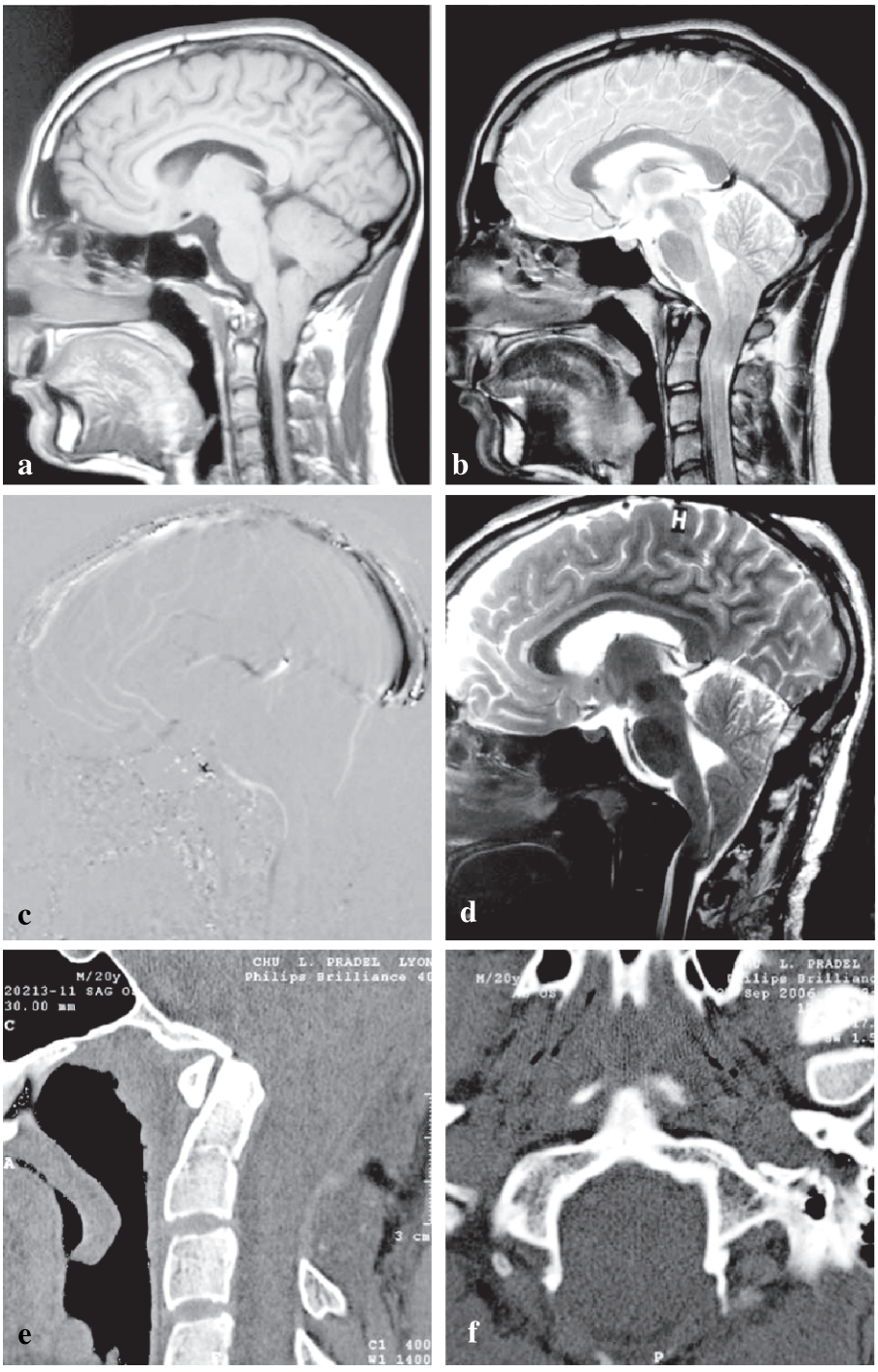
In 1981, Williams [74] used simultaneous measurements to demonstrate a differential pressure gradient between the intraventricular and the lumbar subarachnoid spaces. He later proposed the "craniospinal pressure dissociation theory", which suggests that CSF flow is obstructed in patients with CM-I at the craniocervical junction by the herniated cerebellar tonsils, resulting in a differential pressure gradient between the cranial and spinal cavities [75]. Significant pressure differentials between these two areas occur during the systolic cardiac cycle and Valsalva maneuvers. This effect increases the impact of tonsils at the craniocervical junction, creating a piston effect that drives CSF into the Virchow-Robin and interstitial spaces, thus leading to the formation of syringomyelia [37, 44, 57, 74, 75, 77]. The propagation of syrinx fluid caudally with each heartbeat, leads to syrinx progression [22].

Moreover, cisterna magna functions as a shock absorber against the pulsatile CSF waves coming from the cranial side. Reducing the temporary fluid storage capacity of the cisterna magna dramatically increases the pressure wave propagated along the central canal. The loss of the shock absorbing capacity of the cisterna magna and the subsequent increase of central canal wall pressure leads to syrinx progression in patients with CM-I [8, 44, 73].

Neuro-imaging

Brain and entire spinal cord MRI (magnetic resonance imaging) with T1 and T2 sequences is the modality of choice for evaluating cerebellar tonsils herniation through foramen magnum (Fig. 1a, b, and 3b). Moreover, MRI is able to search and show the associated hydrocephalus and/or syringomyelia degree

Fig. 1. Illustrative case: preoperative sagittal T1 (a) and T2-weighted MRI (b) revealing CM-I with cerebellar tonsils herniated to C-2 posterior arch (Grade IV); Postoperative cine-MRI (c) showing dynamic flow posterior to the cerebellar tonsils; Postoperative T2-weighted MRI (d) with CSF visible posterior to the cerebellar tonsils; Postoperative sagittal CT-scan with craniectomy, C-1 and C-2 laminectomy (e) and axial CT-scan with Foramen Magnum opened laterally condyle to condyle (f); Platybasia can be noted (a–b)


a
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(Fig. 3a and b). In addition, a gadolinium-enhanced MRI is recommended to rule out the existence of any intramedullary tumor. Tonsillar herniations can be classified into four grades, corresponding to the degree to which they have descended through the foramen magnum [60]. Grade I corresponds to a level of tonsils descent between the foramen magnum and C-1, Grade II corresponds to descent to C-1 level, Grade III corresponds to descent to between C-1 and C-2 (Fig. 3b), and Grade IV corresponds to descent to C-2 level (Fig. 1a and b). The radiological assessment often reveals other bone anomalies of the skull base, such as basilar impression, atlanto-occipital fusion, atlanto-axial assimilation, platybasia (Fig. 1a and b), and Klippel-Feil syndrome [10, 35, 56]. Where present, syringomyelia can be classified into four groups. Group I corresponds to the cervical location, Group II to the thoracic location, Group III to the cervicothoracic location and Group IV to panmedullary extension.

Recent advances in MRI permit a cinematic analysis of CSF flow, posterior to the cerebellar tonsils at the foramen magnum (Fig. 1c), plotted in relation to the cardiac cycle, producing a flow velocity profile. A reduction of the flow velocity and a shorter period of caudal CSF flow are typical of CM-I [13]. The same MRI modality can be performed postoperatively to confirm the re-establishment of a normal CSF flow velocity.

Moreover, intraoperative Doppler ultrasonography anatomical and dynamical informations can be used as a guide for performing patient-specific posterior fossa decompressions.

If hydrocephalus is present, shunt insertion or endoscopic ventriculocisternostomy should precede consideration of other surgical intervention.

Overview of the various technical modalities

For more than one-hundred years, various modalities have been employed to manage CM-I decompression. Some authors limit themselves to performing only a simple suboccipital craniectomy, associated with a C-1 ± C-2 laminectomy [27, 40]. Others suggest enlargement of the dura of the posterior fossa in addition to the craniectomy [1, 2, 4, 6, 7, 11, 13, 14, 16–19, 21, 22, 24, 26, 28, 32, 33, 36, 40, 41, 44, 47, 48, 50–54, 60, 61, 63, 64, 68–70, 72]. One option is to incise only the external layer of the dura, leaving the internal layer intact [19, 24, 26, 41]. Another option is to open both layers of the dural sheath, along a vertical line [7], or in a Y-shaped manner [4, 13, 14, 36, 41, 52, 60, 63] and to patch the enlarged opening with a duraplasty of periosteum [4, 53, 60, 68, 69], fascia lata [7, 28], or artificial dura [52] rather than leaving it open [54, 70].

Dural incision may be accompanied by a large arachnoid opening to explore the foramen of Magendie [1–3, 6, 7, 11, 21, 28, 40, 47, 52, 53, 61, 64, 67, 69, 72] in order to ascertain its patency, especially in cases where hydrocephalus is also present, although arachnoid opening predisposes to pseudomeningocele and/or CSF fistulas.

Bilateral resection of the tonsils has been advocated by some authors in order to achieve an optimal decompression of the cervico-occipital junction [3, 7, 13, 17, 21, 48, 76]. A suboccipital cranioplasty is systematically done by Milhorat to cover and protect the duraplasty, and to limit the extent of extradural scarring [36].

In patients with a large-sized syrinx, some authors prefer to use syringo-subarachnoid shunt alone [1, 23, 24, 64, 70].

Recent advances in neuroimaging modalities and the widespread use of MRI has led to CM-I being diagnosed with increased frequency (0.56 [15] to 0.77% [34] of incidence on MRI studies). Therefore, we see many asymptomatic and minimally symptomatic patients with CM-I ± syringomyelia who pose problems of therapeutic strategy.

When CM-I and/or syrinx is/are incidentally identified, there is no scientific proof that they will become symptomatic in the future. Brain and entire spinal cord MRI assessment secures the follow up, because it can identify a radiological aggravation before symptoms are present, thus enabling surgical treatment to be carried out in time.

When performing dural incision and duraplasty, the arachnoid membrane may be opened, but one may prefer to preserve it, which avoids CSF leakage [6, 18, 24, 32, 44, 52, 53, 60, 63]. This is our preferred option when treating patients, and the surgical technique which we describe in more detail here.

Decompression with extreme lateral foramen magnum opening and expansile duraplasty with arachnoid preservation

This technique was carried out in a personal series of 44 adult patients with symptomatic CM-I.

Personal series

From 1990 to 2000, 44 adult patients were operated on using extreme lateral foramen magnum opening and expansile duraplasty with arachnoid preservation. 15 had CM-I with syringomyelia on MRI (34%) and 29 had CM-I without abnormal neuro-imaging of associated syringomyelia (66%). 13 (29%) were males and 31 (71%) females. Age ranged from 14 to 63 years, with the average age being 40. The mean duration of symptoms from origin to surgery was 3 years and 6 months, with extremes of 3 months and 15 years. Presenting symptoms, signs, functional status, and neuro-imaging are listed in Table 1.

Analysis of our results showed that a suboccipital craniectomy and C-1 laminectomy, with extreme lateral foramen magnum decompression, together with dural opening and arachnoid preservation, followed by enlargement duraplasty, was able to obtain improvement in 83% of patients with CM-I alone,

Table 1. *Presenting symptoms (A), signs (B), functional status (C), and neuro-imaging (D) in CM-I, without or with syringomyelia, listed in decreasing order. Personal series [60]*

A – Symptoms			
Pain:	86.4%	unsteadiness	4.5%
–Neck (occipito-cervical)	38.7%	diplopia	2.3%
–Trigeminal neuralgia	20.5%	hypo-acousia	2.3%
–Brachial neuralgia	15.9%	difficulty in swallowing	2.3%
–Headaches	6.8%	vomiting	2.3%
–Backpain	4.5%	micturition imperiosa	2.3%
Paresthesias	29.5%	attacks of unconsciousness	2.3%
Dizziness	18.2%		
B – Signs			
Pinprick altered sensation	27.3%	dysmetry	4.5%
Thermal altered sensation	15.9%	dysarthria	4.5%
Upper extremity weakness	13.6%	facial hemispasm	2.7%
Hand atrophy	9.1%	dysphonia	2.3%
Hyperactive lower reflexes	6.8%	hypopallesthesia	2.3%
Gait disturbances	6.8%	lower extremity weakness	2.3%
Hyperactive upper reflexes	4.5%	babinski sign	2.3%
Micturition imperiosa	4.5%	urinary incontinence	2.3%
C – Functional status (See table: Karnofsky Scale)			
Karnofsky Disability Scale: 37 patients (84%) scored above 70. (24 CM-I alone, and 13 CM-I + S).			
Karnofsky Disability Scale: 7 patients (16%) scored below 70. (5 CM-alone, and 2 CM-I + S).			
D – Neuro-imaging			
29 (66%) had CM-I alone		Tonsillar herniation:	31 patients (71%) Grade I
15 (34%) had CM-I + S:	panmedullary in 6 (40%).		8 patients (18%) Grade II
	cervical in 4 (27%)		3 patients (7%) Grade III
	thoracic in 3 (20%)		2 patients (4%) Grade IV
	cervicothoracic in 2 (13%)		

Table 2. *Postoperative results. Personal series [60]*

		Clinical outcome: N (%)			Syrinx on postoperative MRI			
	N	IMP	STAB	AGG	IMP	STAB	AGG	Complications
CM	29	24 (83)	5 (17)	0 (0)	–	–	–	delayed wound
S	15	12 (80)	3 (20)	0 (0)	9 (60)	6 (40)	0 (0)	healing 5 (12), CSF leak 3 (7)

N Number of patient, *IMP* improved, *STAB* stabilized, *AGG* aggravated, *CM* Chiari type I malformation alone, *S* Chiari malformation with syringomyelia.

Table: Karnofsky Scale

Score	
100	normal; no complaints, no evidence of disease
90	able to carry on normal activity; minor symptoms
80	normal activities with effort; some symptoms
70	cares for self; unable to carry on normal activity
60	requires occasional assistance; cares for most needs
50	requires considerable assistance and frequent care
40	disabled; requires special care and assistance
30	severely disabled; hospitalised, death not imminent
20	very sick; active supportive care needed
10	moribund; fatal processes are progressing rapidly

and in 80% of patients with CM-I associated with syringomyelia. This technique did not provoke any neurological or other severe or lasting associated complication (Table 2).

Technical description

Patients are operated on under general anaesthesia with endotracheal intubation, in the sitting position. All of them previously undergo a Doppler transesophageal echocardiography to exclude a patent foramen ovale. During surgery, each patient is equipped with a right atrial central venous catheter and Doppler ultrasonography to monitor the possible occurrence of air embolism.

The goal of surgery is to re-establish normal patterns of CSF flow, by removing the brainstem compression. The strategy of the surgery is to increase the capacity of the occipito-cervical junction in its two axial-plane diameters (the antero-posterior and the transverse), so as to achieve an optimal decompression of the neural structures and obtain free cisternal spaces with good CSF circulation in the cisterna magna, and also around the brainstem and cervico-occipital junction.

The operation is performed in the sitting position, with the patient's head fixed by a Mayfield® three-pin headholder in a slightly flexed position. After antiseptic preparation, the hair is shaven to 2 cm either side of the incision draw.

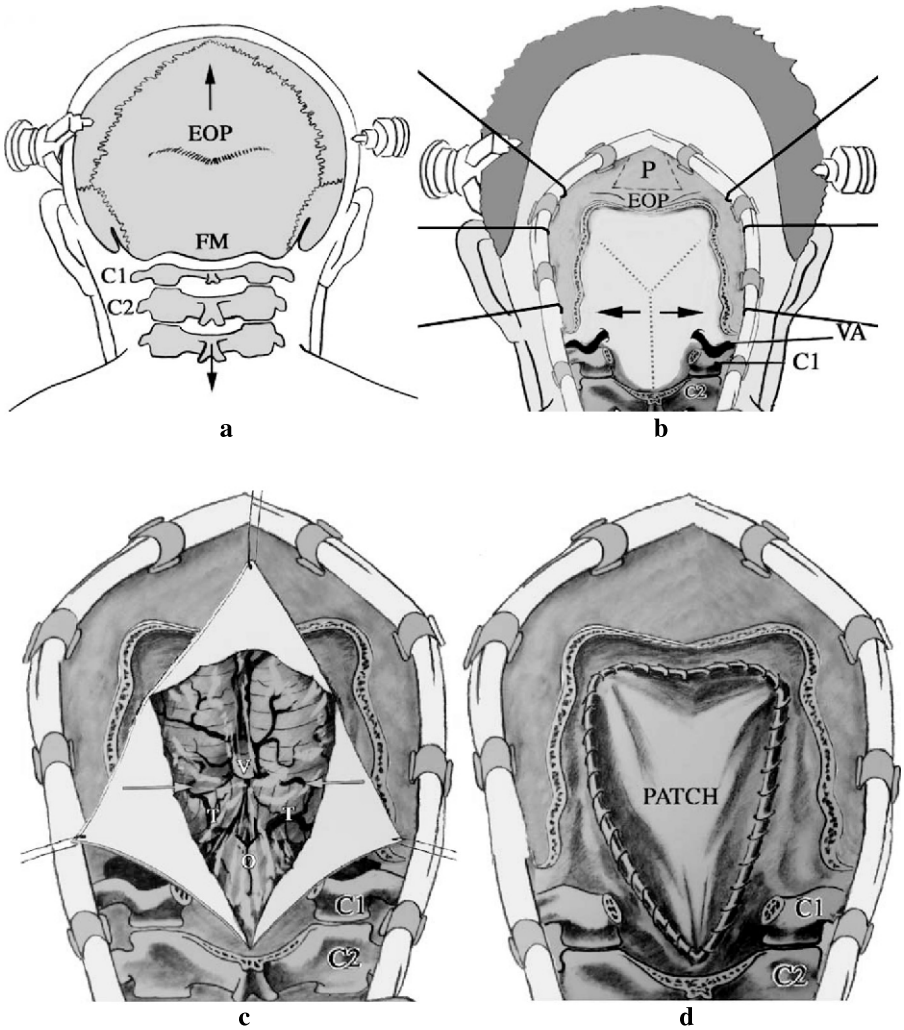

Fig. 2. Technique of cervico-occipital decompression (*schematic drawings*). Surgical steps are: (a) Skin incision (*vertical arrows*); Exposure of bony structures: external occipital process (*EOP*), foramen magnum (*FM*), C-1 and C-2 laminae. (b) Bone opening: sub-occipital craniotomy with extreme lateral opening of Foramen Magnum (*horizontal arrows*); Vertebral artery exposure (*VA*) on both sides; C-1 laminectomy; Periosteum for patching (*P*) above the external occipital process (*EOP*). (c) Y-shaped dural opening with arachnoid preservation; Exposure of herniated tonsils with marked engrooving by the posterior margin of foramen magnum (*arrows*); Obex (*O*), Vermis (*V*), Tonsils (*T*). (d) Enlargement duraplasty with periosteal patch (*PATCH*)

A midline occipito-cervical skin incision is made from 5 cm above the external occipital protuberance (to expose the supra-occipital periosteum), down to the level of the C-4 spinous process (Fig. 2a). The periosteum is preserved in the supra-occipital region so that it can be harvested to patch the dural opening at closure. Then posterior cervical muscles are elevated to expose the occipital bone and foramen magnum, as well as the posterior arch of C-1 in all cases, and where necessary of C-2, depending on the degree of tonsillar herniation. Special care is taken not to damage the occipital nerve on both sides.

The vertebral arteries at occipito-cervical level are identified and protected on both sides. Ligamentum flavum and epidural fat is removed, exposing the dura matter. Particular care has to be taken when disconnecting the dura from the undersurface of the foramen magnum. Once this is done, a sub-occipital craniectomy is made by removing a bone flap, the purpose of which is to decompress posteriorly the medullary-spinal cord junction and the tonsils. When the skull bone is thick, it can be drilled to facilitate the use of the rongeur. The craniectomy is completed with an extreme lateral opening of

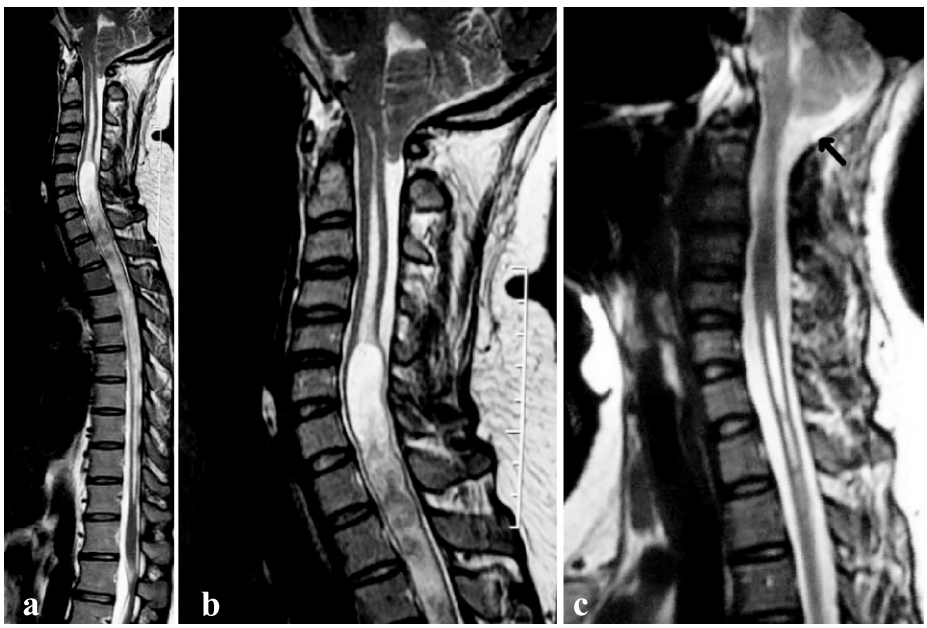

Fig. 3. Illustrative case: Sagittal T2-weighted MRI obtained before (a and b) and after (c) surgery. The cerebellar tonsil appears significantly pointed and inferiorly displaced (b). Effacement of CSF is ventral to the cervicomedullary junction and dorsal to the cerebellar tonsil (b). A large panmedullary syringomyelia is associated with CM-I (a). Three months after bone decompression and duraplasty, the cerebellar tonsil appears more rounded, a new cisterna magna can be seen (*black arrow*) and the resolution of the cervical syrinx is nearly complete (c)

the rim of the foramen magnum by bone resection with Kerrison® rongeurs to the level of the occipital condyles on both sides (Fig. 1f). The aim here is to achieve a good decompression of both tonsils, not only posteriorly but also laterally. The arch of C-1 (and C-2 if necessary) is/are then removed taking care not to compress the underlying dura (Fig. 2b). Even if in most of CM-I tonsils does not reach below C-1, we preferred to remove systematically the arch of C-1 to increase cisterna magna volume and improve its shock absorbing capacity.

A Y-shaped opening is then made to each bone resection limit, in order to enlarge the cisterna magna. Particular care has to be taken when opening both dural leaves at the level of the foramen magnum, because of the usual presence of dural occipital sinuses between the leaves of the dura. If bleeding occurs, it can be controlled by applying titanium clips to obtain definitive hemostasis by compressing the two leaves of the dura together. The arachnoid membrane is preserved to avoid CSF leakage and consequent brain collapse (Fig. 2c). To preserve the arachnoid membrane, the opening of the dura matter is made step by step, placing cottonoids between the dura and arachnoid space to achieve the aperture of both dural leaves. Nevertheless, accidental "pin-points" arachnoids openings resulting in small drops of CSF leakage often occur. However, their small sizes permit cessation within a few seconds.

Then, a duraplasty is made with periosteum patch, harvested from the supra-occipital region, in order to enlarge the posterior fossa and restore a spacious cisterna magna. The dural patch is tightened with three running sutures, in triangular-shaped manner with the base superior (Fig. 2d). Valsalva maneuvers are performed to ensure a watertight closure. Finally, the wound is closed, one layer at a time, muscles, fascia, subcutaneous tissue and skin, with interrupted sutures.

For post-operative care, the patient is placed in the intensive care unit for one night. A cervical collar is offered to the patient to keep his neck comfortable with a physiological lordosis and to reduce the pain. Analgesics and anticoagulation are given systematically. On average the patient is discharged on the 10th day. One month postoperatively, physiotherapy with particular mobilization of both upper limbs is undertaken to avoid frozen shoulders. At 2 months, an outpatient clinic visit is organized before a decision is taken as to the patient's readiness to return to work and resume a normal life.

Discussion from literature review

This technical modality has to be compared with the other varieties of craniocervical decompression techniques. Therefore, we reviewed 211 articles published during the past sixteen years (1990–2006), provided by the PUB-MED system (keywords for search were: Chiari, syrin*, I, decompression). Only 31 reports with information on the techniques used and their corresponding long-

Table 3. *Summary of literature results in CM-I alone, after surgical decompression*

Series	Technical modalities	N	Clinical outcome: N (%)		
			IMP	STAB	AGG
Pillay *et al.* [47]	FMD + DO + AO + DU	14	12 (86)	2 (14)	0 (0)
Bindal *et al*. [6]	FMD + DO + DU	9	9 (100)	0 (0)	0 (0)
Fisher [17]	FMD + DO + AO + RT + DU	3	2 (67)	1 (33)	0 (0)
Klekamp *et al.* [28]	FMD + DO + AO + DU	36	*	–	–
Blagodatsky *et al.* [7]	FMD + DO + AO + DU	16	14 (88)	1 (6)	1 (6)
Munshi *et al.* [40]	FMD + DO + AO + DU	11	10 (91)	1 (9)	0 (0)
	FMD	4	3 (75)	1 (25)	0 (0)
Alperin *et al.* [2]	FMD + DO + AO + DU	2	2 (100)	0 (0)	0 (0)
James and Brant [27]	FMD	3	3 (100)	0 (0)	0 (0)
Sindou *et al.* [60]	FMD + DO + DU	29	24 (83)	5 (17)	0 (0)
Sivaramakrishnan *et al.* [61]	FMD + DO + AO + DU	7	7 (100)	0 (0)	0 (0)
McGirt *et al.* [32]	FMD + DO + DU	17	13 (76)	4 (24)	0 (0)
Sakas *et al.* [54]	FMD + DO + AO + RT	5	2 (40)	3 (60)	0 (0)

IMP Improved, *STAB* stabilized, *AGG* aggravated, *FMD* foramen magnum decompression, *DO* dural opening, *AO* arachnoid opening, *DU* duraplasty, *RT* resection of tonsils.

* In Klekamp *et al.*'s series [28] average Karnofsky score passed from 68 (pre operatively) to 77 (at one year post-operatively) with large craniectomy and from 77 (pre op.) to 83 (at one year post op.) with small craniectomy. Kaplan-Meier analysis demonstrated that 9 of the 36 patients without a syrinx showed progressive worsening of at least some of their symptoms and signs after a mean follow-up of 39 ± 52 months.

term outcomes, were sufficiently detailed to allow comparison between series, and were therefore retained. These are listed in Table 3 for CM-I alone, Table 4 for CM-I with syringomyelia, and Table 5 for both.

In order to evaluate the effectiveness and risks of each of the various techniques, the literature series which corresponded to the same technical modality were grouped together. Separate inventories were made for CM-I alone and CM-I associated with syringomyelia.

Chiari type I malformation without syringomyelia (Tables 3 and 5)

Craniocervical bone resection without dural opening (technique No. 1) was performed in only 7 cases. 6 patients (86%) improved. Foramen magnum decompression with dural opening but with preservation of the arachnoid membrane and duraplasty to enlarge cisterna magna (Technique No. 3) was performed in 55 cases. An improvement was obtained in 84% (Table 3), with very few complications, as shown in Table 5. Systematic opening of the arach-

Table 4. *Summary of literature results in CM-I with syringomyelia, after surgical decompression and/or shunt. Clinical outcome and evolution of syrinx on post-operative MRI*

Series	Technical modalities	N	Clinical outcome			Syrinx on post-op MRI		
			IMP	STAB	AGG	IMP	STAB	AGG
Vaquero *et al.* [70]	FMD + DO + AO	15	4 (27)	6 (40)	5 (33)	14 (93)	1 (7)	0 (0)
	Shunt	15	10 (67)	2 (13)	3 (20)	15 (100)	0 (0)	0 (0)
Pillay *et al.* [47]	FMD + DO + AO + DU	17	9 (53)	6 (35)	2 (12)			
Fujii *et al.* [18]	FMD + DO + DU	5	4 (80)	0 (0)	1 (20)	3 (60)	1 (20)	1 (20)
	FMD + DO + DU + SH	8	8 (100)	0 (0)	0 (0)	6 (75)	2 (25)	0 (0)
Isu *et al.* [26]	FMD + DO (ext. Layer)	7	6 (86)	1 (14)	0 (0)	7 (100)	0 (0)	0 (0)
Tognetti and Calbucci [64]	FMD + DO + AO + DU	17	14 (82)	2 (12)	1 (6)	12 (100)	0 (0)	0 (0)
	Shunt	12	4 (33)	5 (42)	3 (25)	12 (100)	0 (0)	0 (0)
Raftopoulos *et al.* [48]	FMD + DO + AO + RT + DU	8	8 (100)	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)
VanVelthoven *et al.* [67]	FMD + DO + AO + DU	25	10 (40)	9 (36)	6 (24)			
Versari *et al.* [72]	FMD + DO + AO + DU	40	25 (63)	9 (22)	6 (15)	28 (70)	12 (30)	0 (0)
Oldfield *et al.* [44]	FMD + DO + DU	7	5 (71)	2 (29)	0 (0)	7 (100)	0 (0)	0 (0)
Sahuquillo *et al.* [52]	FMD + DO + DU	10	8 (80)	2 (20)	0 (0)			
	FMD + DO + AO + DU	10	2 (20)	5 (50)	3 (30)			
Bindal *et al.* [6]	FMD + DO + AO + DU	12	7 (58)	5 (42)	0 (0)			
Fisher [17]	FMD + DO + AO + RT + DU	16	9 (56)	7 (44)	0 (0)	14 (93)	1 (7)	
Hida *et al.* [24]	FMD + DO (ext. Layer)	12	10 (83)			30 (94)		
	FMD + DO + DU	21	17 (81)	3 (14)	1 (5)			
	Shunt	37	36 (97)			37 (100)	0 (0)	0 (0)
Klekamp *et al.* [28]	FMD + DO + AO + DU	88	*					
Vanaclocha *et al.* [69]	FMD + DO + AO + DU (+ BR)	28	20 (73)	8 (27)	0 (0)	11 (39)		
Gambardella *et al.* [19]	FMD + DO (ext. Layer)	8	7 (87)	0 (0)	1 (13)	7 (87)		

Guyotat *et al.* [21]	FMD + DO + DU	50	18 (36)	14 (28)	18 (36)	14 (58)		
	FMD + DO + AO + RT + DU	8	7 (87)	1 (13)	0 (0)			
	FMD + DO + DU + SH	8	6 (75)	1 (13)	1 (12)			
Aghakhani *et al.* [1]	FMD + DO + AO + DU	242	92 (38)	121 (50)	29 (12)	36 (15)		
	Shunt	31	0 (0)	8 (71)	3 (29)	(7)		
Blagodatsky *et al.* [7]	FMD + DO + AO + DU	44	34 (78)	8 (18)	2 (5)			
	FMD + DO + AO + RT + DU	11	7 (64)	3 (27)	1 (9)			
Sakamoto *et al.* [53]	FMD + DO + DU + BR	20	20 (100)	0 (0)	0 (0)	20 (100)	0 (0)	0 (0)
	FMD + DO + AO + DU + BR	20	17 (85)	3 (15)	0 (0)	20 (100)	0 (0)	0 (0)
	FMD + DO + AO + DU + BR	4	3 (75)	1 (25)	0 (0)	3 (75)	1 (25)	0 (0)
Ellenbogen *et al.* [13]	FMD + DO + AO + RT + DU	51	49 (96)	2 (4)	0 (0)	49 (96)	2 (4)	0 (0)
Ergün [16]	FMD + DO + AO + DU + SH	18	16 (89)	2 (11)	0 (0)	18 (100)	0 (0)	0 (0)
Munshi *et al.* [40]	FMD + DO + AO + DU	12	10 (84)	2 (16)	0 (0)	9 (100)	0 (0)	0 (0)
	FMD	7	5 (71)	2 (29)	0 (0)	3 (50)	0 (0)	3 (50)
Alperin [2]	FMD + DO + AO + DU	1	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Hida and Iwasaki [23]	Shunt	59	59 (100)	0 (0)	0 (0)	59 (100)	0 (0)	0 (0)
James and Brant [27]	FMD	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Sindou *et al.* [60]	FMD + DO + DU	15	12 (80)	3 (20)	0 (0)	9 (60)	6 (40)	0 (0)
Takayasu *et al.* [63]	FMD + DO + DU	16	16 (100)	0 (0)	0 (0)	16 (100)	0 (0)	0 (0)
Sakas *et al.* [54]	FMD + DO + AO + RT	10	4 (40)	6 (60)	0 (0)	7 (70)	2 (20)	1 (10)

MP Improved, *STAB* stabilized, *AGG* aggravated, *FMD* foramen magnum decompression, *DO* dural opening, *AO* arachnoid opening, *DU* duraplasty, *SH* shunt, *RT* resection of tonsils, *BR* bone reconstructed.

* In Klekamp *et al.*'s series [28], Karnofsky score passed from 68 (pre op.) to 74 (at one year post op.) with large craniectomy and from 71 (pre op.) to 77 (at one year post op.) with small craniectomy. Kaplan-Meier analysis demonstrated that 16 of the 88 patients with a syrinx showed progressive worsening with time, but much less with a small craniectomy (14%) than with a large craniectomy (62%). There were actually two groups according to the size of craniectomy. In the group of patients with a small craniectomy the size of the syrinx decreased in 87%, was unchanged in 11% and increased in only 2% (versus 72, 6 and 22%, respectively, in the large craniectomy group).

noid in addition to dural opening (Technique No. 4) was performed in 86 cases. It did not reveal any superiority compared to the procedure without arachnoid opening. The improvement rate was 84% (compared with 84%) and there was 11% of aggravation (versus none). The results achieved with technique No. 3 indicated that dural opening with preservation of arachnoid membrane is preferable, as complications due to arachnoid opening were frequent and sometimes severe, as illustrated by Table 5.

Chiari type I malformation with syringomyelia (Tables 4 and 5)

Results with the various reported techniques are summarized in Tables 4 and 5. Statistical analysis (Confidence Interval 95% CI), showed that foramen magnum decompression with simple incision of the dural outer layer (modality No. 2), or complete dural opening followed by duraplasty (modalities No. 3–5 or 8), were significantly better ($p < 0.05$) than foramen magnum decompression with dural and arachnoid opening, but without duraplasty (modality No. 6 and No. 7). Modalities No. 6 and No. 7 were the worst options.

Interestingly, in a study comparing the effects of two varieties of craniectomy (one small and one large and both associated with dural opening, arachnoid opening and duraplasty) Klekamp *et al.* observed better results with the smaller bone resection. In the group with small craniectomy, syrinx was seen to have decreased in 87% of cases, it was unchanged in 11% of cases and had increased in 2%. This compared with 72%, 6% and 22%, respectively, in the large craniectomy group [28]. Foramen magnum decompression with dural opening and enlargement duraplasty, but without opening the arachnoid (modality No. 3), was the most effective and also the least dangerous modality. With this technique (which was performed in 94 cases), 87% of the patients were improved, whereas only 2% deteriorated either because of, or despite surgery having been performed. Furthermore, the complication rate was minimal, as shown in Table 5.

Bone decompression with dural incision of only the outer layer (modality No. 2), produced only marginally inferior results when compared with complete dural opening. This technique was performed in 27 cases. 85% of the patients showed improvement and 4% deteriorated. Foramen Magnum decompression without any dural opening at all (modality No. 1), was less effective. With this technique, which was performed in only 8 cases, the improvement rate was 75%. In the case of both techniques, complications were nil, as shown in Table 5.

Whether the dura was reconstructed (modalities No. 4 and No. 5), or left open (modality No. 6 and No. 7), opening of the arachnoid was followed by a number of complications. These complications were particularly severe when the dura was not closed, as shown in Table 5. The 7 patients who were reported in the literature as having died from complications [1, 7, 21, 28],

Table 5. *Summary of results in the literature, according to the technical modality used. Clinical outcome [N number; (%)]*

		N	Clinical outcome			Complications
			IMP	STAB	AGG	
1. FMD without DO						
James and Brant [27]	CM	3	3 (100)	0 (0)	0 (0)	
	S	1	1 (100)	0 (0)	0 (0)	
Munshi *et al.* [40]	CM	4	3 (75)	1 (25)	0 (0)	wound
	S	7	5 (71)	2 (29)	0 (0)	infection 1 (9)0
Total	CM	7	6 (86)	1 (14)	0 (0)	
	S	8	6 (75)	2 (25)	0 (0)	
2. FMD with DO (outer)						
Gambardella *et al.* [19]	S	8	7 (88)	0 (0)	1 (12)	
Hida *et al.* [24]	S	12	10 (83)	2 (17)	0 (0)	
Isu *et al.* [26]	S	7	6 (86)	1 (14)	0 (0)	
Total	S	27	23 (85)	3 (11)	1 (4)	
3. FMD + DO + DU (arachnoid integra)						
Bindal *et al.* [6]	CM	9	9 (100)	0 (0)	0 (0)	
Fujii *et al.* [18]	S	5	4 (80)	0 (0)	1 (20)	
Hida *et al.* [24]	S	21	17 (81)	3 (14)	1 (5)	motor deterioration (13)
McGirt *et al.* [32]	CM	17	13 (76)	4 (24)	0 (0)	
Oldfield *et al.* [44]	S	7	5 (71)	2 (29)	0 (0)	
Sahuquillo *et al.* [52]	S	10	8 (80)	2 (20)	0 (0)	aseptic meningitis 1 (5)
Sakamoto *et al.* [53]	S	20	20 (100)	0 (0)	0 (0)	
Sindou *et al.* [60]	CM	29	24 (83)	5 (17)	0 (0)	delayed wound
	S	15	12 (80)	3 (20)	0 (0)	healing 5 (12), CSF leak 3 (7)
Takayasu *et al.* [63]	S	16	16 (100)	0 (0)	0 (0)	
Total	CM	55	46 (84)	9 (16)	0 (0)	
	S	94	82 (87)	10 (11)	2 (2)	
4. FMD + DO + AO + DU						
Aghakhani *et al.* [1]	S	242	92 (38)	121 (50)	29 (12)	wound hematoma 17 (6), meningitis 17 (6)
Alperin *et al.* [2]	CM	2	2 (100)	0 (0)	0 (0)	
	S	1	1 (100)	0 (0)	0 (0)	
Bindal *et al.* [6]	S	12	7 (58)	5 (42)	0 (0)	

(*continued*)

Table 5 (*continued*)

		N	Clinical outcome			Complications
			IMP	STAB	AGG	
Blagodatsky *et al.* [7]	CM	16	14 (88)	1 (6)	1 (6)	
	S	44	34 (78)	8 (18)	2 (5)	
Guyotat *et al.* [21]	S	50	18 (36)	14 (28)	18 (36)	meningitis 1 (1)
Klekamp *et al.* * [28]	CM	36	27	0	9	Infection 5 (4), aseptic meningitis 13 (10), CSF leak 15 (12), hydrocephalus 1 (1), cerebellar 1 (1) and posterior cerebral 1 (1) infarction, apnea 2 (2), mesencephalic disturbances 2 (2) swallowing dysfunction 3 (2)
	S	88	72	0	16	
Munshi *et al.* [40]	CM	11	10 (91)	1 (9)	0 (0)	CSF leak 2 (9), aseptic meningitis 1 (4), subgaleal CSF 4 (17), infection 3 (13), occipital nerve pain 1 (4)
	S	12	10 (84)	2 (16)	0 (0)	
Pillay *et al.* [47]	CM	14	12 (86)	2 (14)	0 (0)	
	S	17	9 (53)	6 (35)	2 (12)	
Sahuquillo *et al.* [52]	S	10	2 (20)	5 (50)	3 (30)	hydrocephalus 1 (10)
Sakamoto *et al.* [53]	S	24	20 (83)	4 (17)	0 (0)	aseptic meningitis 1 (4)
Sivaramakrishnan *et al.* [61]	CM	7	7 (100)	0 (0)	0 (0)	
Tognetti and Calbucci [64]	S	17	14 (82)	2 (12)	1 (6)	
Vanaclocha *et al.* [69]	S	28	20 (73)	8 (27)	0 (0)	
VanVelthoven *et al.* [67]	S	25	10 (40)	9 (36)	6 (24)	
Versari *et al.* [72]	S	40	25 (63)	9 (22)	6 (15)	
Total	CM	86	72 (84)	4 (5)	10 (11)	
	S	610	334 (55)	193 (32)	83 (13)	

(*continued*)

Table 5 (*continued*)

		N	Clinical outcome			Complications
			IMP	STAB	AGG	
5. FMD + DO + AO + RT + DU						
Blagodatsky *et al.* [7]	S	11	7 (64)	3 (27)	1 (9)	
Ellenbogen *et al.* [13]	CM	14	14 (100)	0 (0)	0 (0)	subgaleal CSF 4 (6),
	S	51	49 (96)	2 (4)	0 (0)	CSF leak 2 (9)
Fisher [17]	S	16	15 (94)	1 (6)	0 (0)	aseptic meningitis 2 (11), kyphotic deformity 1 (5), mild hearing loss 1 (5)
Guyotat *et al.* [21]	S	8	7 (87)	1 (13)	0 (0)	meningitis 1 (1)
Raftopoulos *et al.* [48]	S	8	8 (100)	0 (0)	0 (0)	
Williams [76]	S	54	45 (83)	5 (9)	4 (8)	
Total	CM	14	14 (100)	0 (0)	0 (0)	
	S	148	131 (89)	12 (8)	5 (3)	
6. FMD + DO + AO						
Vaquero *et al.* [70]	S	15	4 (27)	6 (40)	5 (33)	cephalalgias 7 (47), meningitis 2 (13), neuralgia Vth 1 (7)
Total	S	15	4 (27)	6 (40)	5 (33)	
7. FMD + DO + AO + RT						
Sakas *et al.* [54]	CM	5	2 (40)	3 (60)	0 (0)	arachnoid adhesions and tethering 3 (20)
	S	10	4 (40)	6 (60)	0 (0)	
Total	CM	5	2 (40)	3 (60)	0 (0)	
	S	10	4 (40)	6 (60)	0 (0)	
8. FMD + DO + DU + SH						
Ergün *et al.* [16]	S	18	16 (89)	2 (11)	0 (0)	aseptic meningitis 2 (11), transient dysesthesias 4 (22)
Fujii *et al.* [18]	S	8	8 (100)	0 (0)	0 (0)	
Guyotat *et al.* [21]	S	8	6 (75)	1 (13)	1 (12)	
Total	S	34	30 (88)	3 (9)	1 (3)	

(*continued*)

Table 5 (*continued*)

		N	Clinical outcome			Complications
			IMP	STAB	AGG	
9. Shunt						
Aghakhani *et al.* [1]	S	31	7 (23)	15 (48)	9 (29)	
Hida *et al.* [24]	S	37	36 (97)	1 (3)	0 (0)	shunt malfunction 4 (11)
Hida and Iwasaki [23]	S	59	59 (100)	0 (0)	0 (0)	shunt malfunction 10 (17)
Tognetti and Calbucci [64]	S	12	4 (33)	5 (42)	3 (25)	leg dysesthesia 1 (8)
Vaquero *et al.* [70]	S	15	10 (67)	2 (13)	3 (20)	leg dysesthesia 8 (53)
Total	S	154	116 (75)	23 (15)	15 (10)	

IMP Improved, *STAB* stabilized, *AGG* aggravated, neuro neurological, *CM* Chiari type I malformation alone, *S* Chiari malformation with syringomyelia, *FMD* foramen magnum decompression, *DO* dural opening, *AO* arachnoid opening, *DU* duraplasty, *SH* shunt, *RT* resection of tonsils.

* For Klekamp *et al.*'s series see legends of Tables 3 and 4 for interpretation.

had large arachnoid openings. Opening of the arachnoid did not guarantee a more effective outcome as shown in Table 5. On the contrary, with technical modality No. 4, only 55% of the 610 patients improved, and in 13% their conditions worsened. The outcome was worst with modality No. 6 and No. 7 (25 patients reported), in which there was improvement in only 32% of cases, stabilization in 48% and aggravation in 20%.

Plugging the obex in addition to arachnoid opening (which we found reported in 106 patients in the literature [7, 47, 53, 67]), did not bring about any positive effect. The improvement rate was 66% and the aggravation rate was 9% (not shown in the table).

It appears from data in the literature that complementary tonsillar resection (modality No. 5), did not bring any significant improvement compared to Foramen Magnum decompression with enlargement duraplasty only. The improvement was obtained in 89% of the 148 patients and there was aggravation in 3% (compared with 87% and 2% with modality No. 3 for example). The same holds true for shunting in addition to foramen magnum decompression with duraplasty (modality No. 8); improvement was achieved in 88% of the 30 patients and aggravation occurred in 3% [1, 24, 64, 70].

Several authors [22, 36, 44, 58, 77] state that they use intraoperative colour doppler ultrasonography to adjust surgical procedure on the basis of real-time anatomic and physiological measurements. They first practice an occipital craniectomy $\pm$ a C-1 laminectomy. An intraoperative ultrasound device is then

positioned so that the neuroradiologist can examine the craniocervical junction. Decompression is considered adequate when a CSF space is present anterior to the brainstem and dorsal to the cerebellar tonsils, and when there is no evidence of abnormal tonsillar piston activity. When decompression is inadequate, a more invasive type of surgery is performed, with duraplasty, tonsillar shrinkage, and/or more laminectomy.

In our experience, we have not been confronted with a symptomatic slump of the hindbrain following craniocervical decompression. Nevertheless, this complication is well-known and as such the clinician must be attentive to the possibility of it occurring, especially in case of large craniectomy and excessive enlargement duraplasty. Intractable headache and/or neurological deficits due to persistent or recurrent syringomyelia should evoke the diagnosis. Holly *et al.* suggest partial suboccipital cranioplasty, with or without intradural exploration, as an effective treatment for this condition [25].

Conclusion

- Foramen magnum decompression with extreme lateral rim resection, followed by dural enlargement, was revealed to be the most effective treatment for CM-I whether associated with syringomyelia or not. As pointed out by Klekamp *et al.* [28], small craniectomy offers better results than large craniectomy.
- Preservation of the arachnoid membrane, whenever there is no evidence of obstruction of the foramen of Magendie and/or arachnoiditis, decreases the risk of complications. That is to say the arachnoid should be dissected in cases of CM-I with syringomyelia and/or hydrocephalus, whenever simple decompression is unlikely to be sufficient to re-establish a good CSF flow, when there is evidence of blocking arachnoiditis.
- Tonsillar resection does not seem to add much value, provided foramen magnum decompression is performed not only posteriorly but also laterally, condyle to condyle.
- Large opening of the arachnoid, with exploration of the foramen of Magendie, and complementary subpial resection of the tonsils, may be considered as a secondary option in the rare cases in which CSF circulation at the cervico-occipital junction is judged to remain insufficient.
- Plugging the obex not only brings no positive benefit, it also entails significant additional risks.
- Syringomyelia associated to CM-I must be treated by craniocervical decompression alone.
- Shunting no longer appears to be an appropriate method of treatment for syringomyelia considered in relation to a dysfunctioning circulation due to CM-I.
- Intraoperative ultrasonography may help to find the least invasive but most effective surgical modality. Nevertheless, further evaluations are needed.

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Vagal nerve stimulation – a 15-year survey of an established treatment modality in epilepsy surgery

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With 2 Figures and 4 Tables

Contents

Abstract

Neurostimulation is an emerging treatment for neurological diseases. Electrical stimulation of the tenth cranial nerve or vagus nerve stimulation (VNS) has

become a valuable option in the therapeutic armamentarium for patients with refractory epilepsy. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment. Vagus nerve stimulation reduces seizure frequency with >50% in 1/3 of patients and has a mild side effects profile.

Research to elucidate the mechanism of action of vagus nerve stimulation has shown that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers. Crucial brainstem and intracranial structures include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures. Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA but also serotoninergic and adrenergic systems. This manuscript reviews the clinical studies investigating efficacy and side effects in patients and the experimental studies aiming to elucidate the mechanims of action.

Keywords: Refractory epilepsy; neurostimulation; vagus nerve stimulation; epilepsy surgery.

Introduction

Epilepsy affects 0.5–1% of the population and is therefore the second most common chronic neurological disease following cerebrovascular disorders [1]. More than 30% of all epilepsy patients have uncontrolled seizures or unacceptable medication-related side effects despite adequate pharmacological treatment [2]. In these patients a thorough diagnostic and therapeutic work-up in a specialised epilepsy center is warranted. Few therapeutic options are available for patients with refractory epilepsy. Epilepsy surgery aims at the removal of the ictal onset zone. It is an invasive treatment option resulting in seizure freedom in up to 85% of the patients depending on the localization of the seizure focus [3]. Due to strict criteria during the presurgical evaluation protocol a large number of patients are considered unsuitable candidates [4]. In these patients a circumscribed, unifocal ictal onset cannot be identified or the ictal onset zone is localized in functional brain tissue as demonstrated by the Wada-test and functional MRI [5].

The inability to adequately treat all patients with refractory epilepsy provides a continuous impetus to investigate novel forms of treatment. Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to or in the neighbourhood of nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Different types of neurostimulation exist depending on the part of the nervous system that is being affected and the way this stimulation is being administered.

Electrical stimulation of the tenth cranial nerve or vagus nerve stimulation (VNS) is an extracranial form of neurostimulation that was developed in the

eighties. In the past decade it has become a valuable option in the therapeutic armamentarium for patients with refractory epilepsy and it is currently routinely available in epilepsy centers worldwide. Through an implanted device and electrode, electrical pulses are administered to the afferent fibers of the left vagus nerve in the neck. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment [6].

The first vagus nerve stimulator was implanted in humans in 1989. However, the historical basis of peripheral stimulation for treating seizures dates back to centuries ago. In the sixteenth and seventeenth century physicians described the use of a ligature around the limb in which a seizure commences to arrest its progress. This method was described by the ancient Greek author Pelops for whom this observation was proof that epileptic fits originated from the limb itself. This hypothesis was reviewed in the beginning of the nineteenth century when Odier and Brown-Séquard showed that ligatures are equally efficacious in arresting seizures caused by organic brain disease e.g. a brain tumor [7]. At the end of this century Gowers attributed these findings to a raised resistance in the sensory and motor nerve cells in the brain that correspond with the limb involved. This would in turn arrest the spread of the discharge. Gowers also reported several other ways by which sensory stimulation could prevent seizures from spreading e.g. pinching of the skin and inhalation of ammonia [8]. Almost a hundred years later Rajna and Lona demonstrated that afferent sensory stimuli can abort epileptic paroxysms in humans [9].

The vagus nerve is a mixed cranial nerve that consists of ∼80% afferent fibers originating from the heart, aorta, lungs and gastrointestinal tract and of ∼20% efferent fibers that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and the pharynx [10–12]. Somata of the efferent fibers are located in the dorsal motor nucleus and nucleus ambiguus respectively. Afferent fibers have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract (NTS). At the cervical level the vagus nerve mainly consists of small diameter unmyelinated C-fibers (65–80%) and of a smaller portion of intermediate-diameter myelinated B-fibers and large-diameter myelinated A-fibers. The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain as well as the brain stem including important areas for epileptogenesis such as the amygdala and the thalamus. There are direct neural projections into the raphe nucleus, which is the major source of serotonergic neurons and indirect projections to the locus coeruleus and A5 nuclei that contain noradrenegic neurons. Finally, there are numerous diffuse cortical connections. The diffuse pathways of the vagus nerve mediate important visceral reflexes such as coughing, vomiting, swallowing, control of blood pressure and heart rate. Heart

rate is mostly influenced by the right vagus nerve that has dense projections primarily to the atria of the heart [13]. Relatively few specific functions of the vagus nerve have been well characterised. Figure 1 depictures a schematic

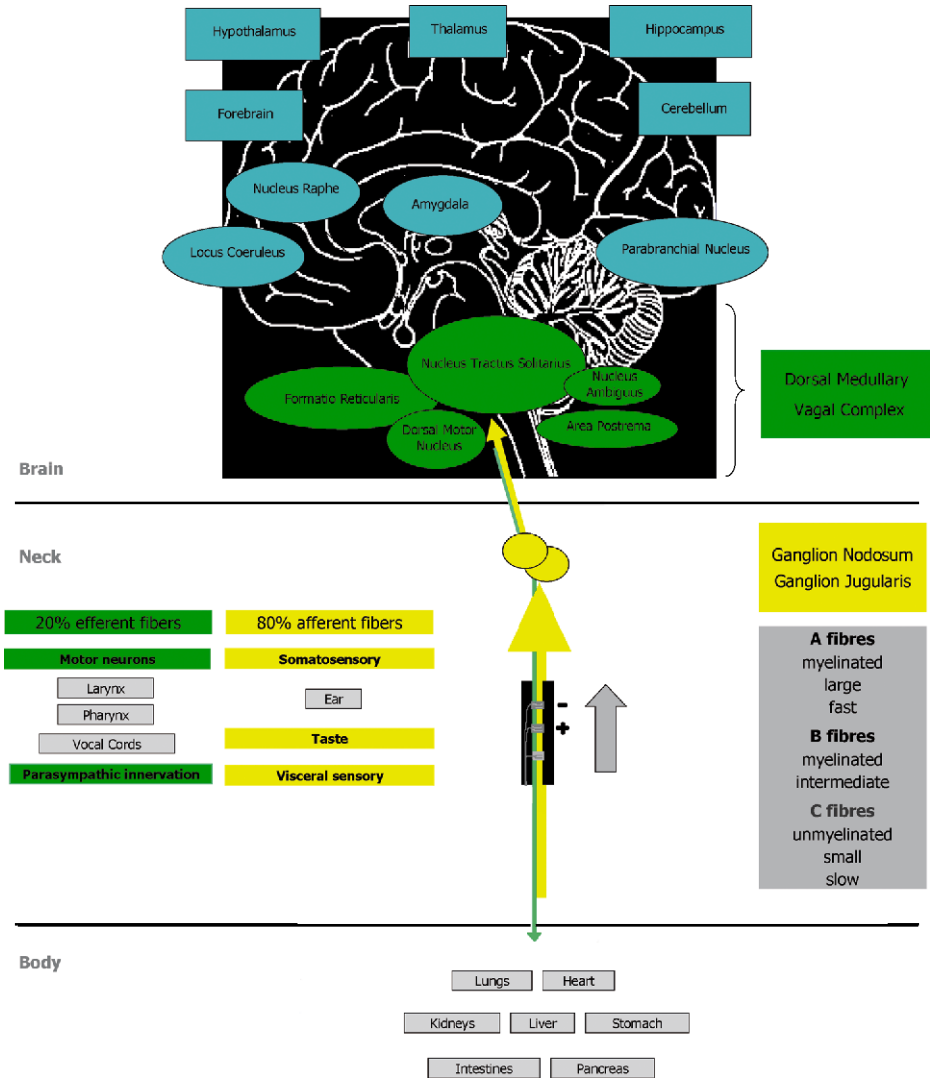

Fig. 1. Schematic drawing of the vagus nerve anatomy. Structures of importance for the mechanism of action in the brain and brain stem: locus coeruleus [23], thalamus [21], temporal lobe structures [21, 31]. Vagus nerve stimulation aims at inducing action potentials within the different types of fibers that constitute the nerve at the cervical level. Unidirectional stimulation of afferent vagal fibers is preferred as epilepsy is considered a disease with cortical origin and efferent stimulation may cause side effects of innervated internal organs

drawing of the vagus nerve anatomy and structures demonstrated to play a role in the mechanism of action.

The vagus nerve is often considered protective, defensive, relaxing. This primary function is exemplified by the lateral line system in fish, the early precedent of the autonomic nervous system. The control of homeostatic functions by the central nervous system in these earlier life forms was limited to the escape and the avoidance of perturbing stimuli or suboptimal conditions. Its complex anatomical distribution has earned the vagus nerve its name, as vagus is the Latin word for wanderer. These two facts together inspired Andrews and Lawes to suggest the name "great wandering protector" [14].

Mechanism of action

Since the first human implant of the VNS Therapy^{TM} device in 1989, over 50,000 patients have been treated with VNS worldwide. As for many antiepileptic treatments, clinical application of VNS preceded the elucidation of its mechanism of action (MOA). Following a limited number of animal experiments in dogs and monkeys, investigating safety and efficacy, the first human trial was performed [15]. The basic hypothesis on the MOA was based on the knowledge that the tenth cranial nerve afferents have numerous projections within the central nervous system and that in this way action potentials generated in vagal afferents have the potential to affect the entire organism [16]. To date the precise mechanism of action of VNS and how it suppresses seizures remains to be elucidated. Crucial questions with regards to the MOA of VNS occur at different levels. Vagus nerve stimulation aims at inducing action potentials within the different types of fibers that constitute the nerve at the cervical level. The question remains, what fibers are responsible and/or necessary for its seizure-suppressing effect. Unidirectional stimulation, activating afferent vagal fibers, is preferred as epilepsy is considered a disease with cortical origin and efferent stimulation may cause side effects. The next step is to identify central nervous system structures located on the anatomical pathways from the cervical part of the vagus nerve up to the cortex, that play a functional role in the MOA of VNS. These could be central gateway or pacemaker function structures such as the thalamus or more specific targets involved in the pathophysiology of epilepsy such as the limbic system or a combination of both. Another issue concerns the identification of the potential involvement of specific neurotransmitters. The intracranial effect of VNS may be based on local or regional GABA increases or glutamate and aspartate decreases or may involve other neurotransmitters that have been shown in the past to have a seizure threshold regulating role such as serotonine and norepinephrine [17]. When considering the efficacy of a given treatment in epilepsy, a certain hierarchical profile of the treatment can be distinguished. A treatment can have

pure anti-seizure effects meaning that it can abort seizures. To confirm such an effect the treatment is most often administered during an animal experiment in which the animals are injected with a proconvulsant compound followed by the administration of the treatment under investigation. A treatment can have a true preventative or so-called anti-epileptic effect. Antiepileptic efficacy implicates that a treatment can prevent seizures, as the main characteristic of the disease namely the unexpected recurrence of seizures is prevented from happening. A treatment can also have an antiepileptogenic effect. This implies that the treatment reverses the development of a pathological process that may have evolved over a long period of time. Such a treatment is clearly protective and may even be used for other neuroprotective purposes. Research directed towards investigating the antiseizure, antiepileptic and potential antiepileptogenic properties of VNS as well as towards the identification of involved fibers, intracranial structures and neurotransmitter systems has been performed. Animal experiments and research in humans treated with VNS have comprised electrophysiological studies (EEG, EMG, EP), functional anatomic brain imaging studies (PET, SPECT, fMRI, c-fos, densitometry), neuropsychological and behavioural studies. Also from the extensive clinical experience with VNS interesting clues concerning the MOA of VNS have arisen. More recently the role of the vagus nerve in the immune system has been investigated. From the extensive body of research on the MOA, it has become conceivable that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers [18, 19]. Unilateral stimulation influences both cerebral hemispheres, as shown in several functional imaging studies [20, 21]. Crucial brainstem and intracranial structures have been identified and include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures [22–25]. Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA but also serotoninergic and adrenergic systems [26, 27]. More recently, Neese *et al.* found that VNS following experimental brain injury in rats protects cortical GABAergic cells from death [28]. A SPECT study in humans before and after 1 year of VNS showed a normalisation of GABAA receptor density in the individuals with a clear therapeutic response to VNS [29]. Follesa *et al.* showed an increase of norepinephrine concentration in the prefrontal cortex of the rat brain after acute VNS [30]. An increased norepinephrine concentration after VNS has also been measured in the hippocampus [31] and the amygdala [32, 33]. Currently, VNS as a neuroimmunomodulatory treatment is being explored. As the vagus nerve plays a critical role in the signalisation and modulation of inflammatory processes, the so-called anti-inflammatory pathway, this could represent a new modality in the MOA of VNS for epilepsy [33, 34].

Early animal experiments in acute seizure models suggest an anti-seizure effect of VNS. McLachlan found that applying VNS at the beginning of a PTZ-

induced seizure significantly shortened the seizure [35]. Woodbury described the beneficial effect of VNS in preventing or reducing PTZ-induced clonic seizures and electrically-induced tonic-clonic seizures in rats [36]. Zabara found that VNS interrupts or abolishes motor seizures in canines induced by strychnine [37]. In our own group, VNS significantly increased the seizure threshold for focal motor seizures in the cortical stimulation model [38]. Also in the human literature, evidence exists that VNS may exert an acute abortive effect. The magnet feature allows a patient to terminate an upcoming seizure [39]. Also, a few case reports describe the use of VNS for refractory SE in pediatric and adult patients [40, 41]. A recent study investigated the effects of acute VNS on cortical excitability by using transcranial magnetic stimulation (TMS) [42]. However, in the clinical trials with VNS, many patients did not regularly self-trigger the device at the time of a seizure and still showed good response to VNS. Moreover, VNS is administered in an intermittent way and it appears that seizures occurring during the VNS off-time are also affected. This intermittent way of stimulation is insufficient to explain the reduction of seizures on the basis of abortive effects alone and suggests a true preventative or so-called anti-epileptic effect of VNS. The fact that VNS influences seizures at a time when stimulation is in the off-mode has also been shown in many animal and human experiments. Already in 1985, Zabara reports that seizure control was extended well beyond the end of the stimulation period. Stimulation for one minute could produce seizure suppression for 5 min [37, 43]. Naritoku *et al.* showed that VNS pretreatment during 1 and 60 min, prior to administration of the seizure triggering stimulation, significantly reduced the duration of behavioural seizures and the duration of afterdischarges in amygdala kindled rats [44]. In a study of Takaya *et al.* VNS was discontinued before induction of PTZ-seizures that were significantly shortened in duration. Moreover, repetition of stimuli increased VNS efficacy suggesting that efficacy of intermittent stimulation improves with long-term use [45]. Zagon *et al.* found that VNS-induced slow hyperpolarization in the parietal cortex of the rat outlasted a 20 s VNS train with 15 s [19]. McLachlan *et al.* found that interictal spike frequency was significantly decreased or abolished after 20 s of VNS in rats for a variable duration, usually around 60 s to 3 min after stimulation discontinuation [46]. Recent data in human EEG studies show a decrease in interictal epileptiform discharges, both in an acute form and after long-term follow-up [47, 48]. The fact that seizures reoccur after end of battery life has been reached is a strong argument against VNS having an antiepileptogenic effect. However, as progress in the development of more relevant animal models for epilepsy has been made, the antiepileptogenic potential of neurostimulation in general is being fully explored and some promising results have been reported e.g. in the kindling model [44, 49]. In human literature, one case report described long-lasting seizure control after explantation of the VNS device [50]. The basis for

Table 1. *Controlled clinical trials*

Reference	Type of study	Nr. of patients	Efficacy	Stimulation related side-effects	Non-stimulation related side-effects	Follow-up (months)
Holder LK *et al.* (1992) Treatment of refractory partial seizures: preliminary results of a controlled study. Pacing and Clinical Electrophyisology 15(10): 1557–71	preliminary results EO3-study randomized double blind active control	37	HIGH stimulation group: 33% mean SF reduction LOW stimulation group: 8.4% mean SF reduction			3
Ben-Menachem E *et al.* (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia 35(3): 616–26	EO3-study randomized double blind active control multicenter	67	HIGH stimulation group (n = 31): 31% mean SF reduction LOW stimulation group (n = 36): 11% mean SF reduction			3
Ramsay RE *et al.* (1994) Vagus nerve stimulation for treatment of partial seizures 2. Safety, side-effects and tolerability. Epilepsia 35: 627–36	EO3-study randomized double blind active control multicenter	67		Hoarseness (36%), Coughing (14%) Throat pain (13%)		3

The Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 45: 224–30	EO3-study randomized double blind active control multicenter	114	HIGH stimulation group (n = 54): 25% mean SF reduction LOW stimulation group (n = 60): 6% mean SF reduction	Hoarseness (37%) Throat pain (11%) Coughing (7%)	Left vocal cord paralysis due to device malfunctioning (1/31)	3
Handforth A *et al.* (1998) Vagus nerve stimulation therapy for partial onset seizures. A randomized, active control trial. Neurology 51: 48–55	EO5-study randomized double blind active control multicenter	196	HIGH stimulation group (n = 94): 28% mean SF reduction LOW stimulation group (n = 102): 15% mean SF reduction	Voice alteration (66%) Cough (45%) Pharyngitis (35%) Pain (28%) Dyspnea (25%)	Left vocal cord paralysis (2), lower facial muscle paresis (2), infection (3)	3

the combined acute and more chronic effects of VNS most likely involves recruitment of different neuronal pathways and networks. The more chronic effects are thought to be a reflection of modulatory changes in subcortical site-specific synapses with the potential to influence larger cortical areas. In the complex human brain these neuromodulatory processes require time to build up. Once installed, certain antiepileptic neural networks may be more easily recruited, e.g. by changing stimulation parameters that may then be titrated to the individual need of the patient. This raises hope for potential anti-epileptogenic properties of VNS using long-term optimized stimulation parameters that may affect and potentially reverse pathological processes that have been installed over a long period of time. However, from a clinical point of view, up till now VNS cannot be considered a curative treatment.

Clinical efficacy and safety

Randomised controlled trials (Table 1)

The first descriptions of the implantable VNS Therapy™ system for electrical stimulation of the vagus nerve in humans appeared in the literature in the early ninetees [51, 52]. At the same time initial results from single-blinded pilot clinical trials (phase-1 trials EO1 and EO2) in a small group of patients with refractory complex partial seizures who were implanted since November 1988 in three epilepsy centers in the U.S.A. were reported [15, 53, 54]. In 9/14 patients treated for 3–22 months a reduction in seizure frequency of at least 50% was observed. One of the patients was seizure-free for more than 7 months. Some patients reported less severe seizures with briefer ictal and postictal periods. Complex partial seizures, simple partial seizures as well as secondary generalized seizures were affected. It was noticed that a reduction in frequency, duration and intensity of seizures lagged 4–8 weeks after the initiation of treatment [15]. In 1993, Uthman *et al.* reported on the long-term results from the EO1 and EO2 study [55]. Fourteen patients had now been treated for 14–35 months. There was a mean reduction in seizure frequency of 46%. Five patients had a seizure reduction of at least 50%, of whom 2 experienced long-term seizure freedom. In none of the patients VNS induced seizure exacerbation. It appeared that three types of responses to vagal stimulation occurred: rapid-sustained, gradual and non-response. In the meantime, two prospective multicenter ($n = 17$) double-blind randomised studies (EO3 and EO5) were started [56, 57]. In these two studies patients over the age of 12 with partial seizures were randomised to a HIGH or LOW stimulation paradigm. The parameters in the HIGH stimulation group (output: gradual increase up to 3.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off) were those believed to be efficacious based on animal data and the initial human pilot studies. Because patients can sense stimulation, the LOW stimulation parameters (output: single increase to

Table 2. *Open long-term prospective clinical trials*

Reference	Type of study	Epilepsy type	Outcome measures	Efficacy at max. FU	Nr. of patients	FU (months)
Holder L *et al.* (1993) J Epilepsy 6: 206–14	open extension EO3	partial	efficacy safety and side-effects		37	18
George R *et al.* (1994) Epilepsia 35(3): 637–43	open extension EO3	partial	efficacy safety and side-effects	Mean SF reduction 38–52%	67	18
Salinsky MC *et al.* (1996) Arch Neurol 53: 1176–80	open extension EO3	partial	efficacy	Mean SF reduction 32%	100	12
Morris GL, Mueller WM. (1999) Neurology 53: 1731–35	open extension EO1–EO5	partial generalized seizures	efficacy safety and side-effects medication treatment	Mean SF reduction 44%	440	36
Ben-Menachem E *et al.* (1999) Neurology 52: 1265–67	open long-term	partial idiopathic generalized symptomatic generalized	efficacy	Responder rate 44%	64	3–64
DeGiorgio CM *et al.* (2000) Epilepsia 41(9): 1195–200	open extension EO5	partial generalized seizures	efficacy	Mean SF reduction 45%	195	12–15
Chavel SM *et al.* (2003) Epilepsy and Beh 4: 302–09	open long-term	partial	efficacy quality of life, depression and anxiety	Responder rate 12m: 54% Responder rate 24m: 61%	30	12–24
Vonck K *et al.* (2004) J Clin Neurophysiol 21: 283–89	open long-term 2-center	partial idiopathic generalized symptomatic generalized	efficacy safety and side-effects	Mean SF reduction 55%	118	6–94
Hui Che Fai A *et al.* (2004) Chin Med J 117(1): 58–61	open long-term	partial symptomatic generalized	efficacy safety and side-effects	Mean SF reduction 40%	13	18

point of patient perception, no further increase, 1 Hz, 130 μs, 30 s on, 3 h off) were chosen to provide some sensation to the patient in order to protect the blinding of the study. LOW stimulation parameters were believed to be less efficacious and the patients in this group represented an active control group. The results of EO3 in 114 patients were promising with a decrease in seizures of 24% in the HIGH stimulation group versus 6% in the LOW stimulation group after 3 months of treatment [56]. The number of patients was insufficient to achieve Food and Drug Administration (FDA) approval leading to the EO5 study in the U.S.A. including 196 patients. 94 patients in the HIGH stimulation group had a 28% decrease in seizure frequency versus 15% in patients in the LOW stimulation group [57].

Prospective clinical trials with long-term follow-up (Table 2)

The controlled EO3 and EO5 studies had their primary efficacy end-point after 12 weeks of VNS. Patients who ended the controlled trials were offered enrolment in a long-term (1–3 years of FU) prospective efficacy and safety study. Patients belonging to the LOW stimulation groups were crossed-over to HIGH stimulation parameters. In all published reports on these long-term results increased efficacy with longer treatment was found [58–62]. In these open extension trials the mean reduction in seizure frequency increased up to 35% at one year and up to 44% at two years of FU. After that improved seizure control reached a plateau [60]. In the following years, other large prospective clinical trials were conducted in different epilepsy centers worldwide. In Sweden, long-term follow-up in the largest patient series (n = 67) in one center not belonging to the sponsored clinical trials at that time, reported similar efficacy rates with a mean decrease in seizure frequency of 44% in patients treated up to 5 years [63]. A joint study of 2 epilepsy centers in Belgium and the USA included 118 patients with a minimum follow-up duration of 6 months. They found a mean reduction in monthly seizure frequency of 55% [64]. In China a mean seizure reduction of 40% was found in 13 patients after 18 months of VNS [65].

Prospective clinical trials in children

There are no controlled studies of VNS in children, but many epilepsy centers have reported safety and efficacy results in patients less than 18 years of age in a prospective way. All these studies report similar efficacy and safety profiles compared to findings in adults [66–69]. Rare adverse events, unique to this age group, included drooling and increased hyperactivity [70]. In children with severe mental retardation and pre-VNS dysphagia, swallowing problems might occur. Switching off the stimulator by applying the magnet over the device during meals may be helpful in such events [71]. In children with epileptic

encephalopathies efficacy may become evident only after >12 months of treatment [72]. A recent Korean multicenter study evaluated long-term efficacy in 28 children with intractable epilepsy. In half of the children there was a >50% seizure reduction after a FU of at least 12 months [73].

In our own prospective analysis of 118 patients, 13 children with a mean age of 12 years (range: 4–17 years) were included with similar efficacy rates and without specific side effects [74].

Clinical trials in specific patient groups

Generalized epilepsy

The clinical studies EO1, EO2, EO3 and EO5 included patients with partial epilepsy. This is a reflection of the fact that patients considered for treatment with VNS were initially evaluated for resective surgery, the preferred treatment for partial epilepsy, but turned out to be unsuitable surgical candidates. The open label longitudinal multicenter (n = 24) EO4 study also included patients with generalized epilepsy [75, 76]. In these patients overall seizure frequency reduction was 46%. Generalized tonic seizures responded significantly better than generalized tonic-clonic seizures. Quintana *et al.* [77], Michael *et al.* [78]. and Kostov *et al.* [79] described in a retrospective way that primary generalized seizures and generalized epilepsy syndromes responded equally well to VNS compared to partial epilepsy syndromes. A prospective study of Holmes *et al.* in 16 patients with generalized epilepsy syndromes and stable AED regimens showed an overall mean seizure frequency reduction of 43% after a follow-up of at least 12 months [80]. Ben-Menachem *et al.* included 9 patients with generalized seizures in a prospective long-term FU study. Especially the patients with absence epilepsy had a significant seizure reduction [63].

Status epilepticus

A few case-reports describing the use of VNS for refractory SE in pediatric and adult patients are available in the literature. Malik *et al.* reported on 3 children with pharmacoresistant SE who were successfully treated with VNS [40]. It was not specified whether the status was convulsive or nonconvulsive in these patients. Winston *et al.* reported a case of a 13-year old boy in whom VNS interrupted a convulsive SE immediately after stimulation was started [81]. Pathwardan *et al.* described a case of a 30-year old man with medically intractable seizures due to severe allergic reactions to multiple AEDs with subsequent evolvement into refractory SE. He underwent VNS treatment after nearly 9 days of barbiturate-induced coma. Stimulation was initated in the operating room. In the following days EEG revealed resolution of previously

observed periodic lateralized epileptiform discharges with the stimulator programmed at 1 mA and a duty cycle of 30 s on and 3 min off. The patient became seizure-free [82]. Zimmerman *et al.* reported on 3 adult patients in whom refractory non-convulsive SE due to AED withdrawal was treated with VNS. After implantation of the device, stimulation output was rapidly increased to 3 mA in the 3 patients. Time to termination of the SE was 3–5 days [83]. A case of our own group described the use of VNS in a 7-year old child with a medically refractory non-convulsive SE [41].

Lennox-Gastaut syndrome

A few studies are available in literature specifically describing the use of VNS in patients diagnosed with Lennox-Gastaut syndrome. One prospective study in 16 patients with Lennox-Gastaut (FU = 6 months) found that ¼ of patients had a >50% reduction in seizure frequency which is comparable to the response rates in the controlled studies, that included few patients with LGS [84]. Other prospective studies reported higher responder rates with a >50% seizure frequency reduction in half of the patients (n = 13, FU = 6 months) [85], in 6/7 patients (FU = 6 months) [86] and in 7/9 patients (FU = 1–35 months) [87]. A retrospective multicenter study that included 46 patients with LGS for efficacy analysis, reported responder rates of 43% [88].

Other patient groups

There have been many reports on various other seizure types and syndromes such as seizures in patients with hypothalamic hamartomas [89], tuberous sclerosis [90], progressive myoclonic epilepsy [91, 92], Landau Kleffner syndrome [93], Asperger syndrome [94], epileptic encefalopathies [72] and syndromes with developmental disability and mental retardation [95–97]. All these studies reported good efficacy with regard to controlling seizures as well as other disease-related symptoms such as cerebellar dysfunction, behavioural and mood disturbances [72, 89, 91, 93, 96]. One study in children with infantile spasms reported less favourable results with long-term benefit in only 2/10 patients and with 4 patients who interrupted VNS due to behavioural problems [98]. A recent report on the efficacy of VNS in 5 children with mitochondrial electron transport chain deficiencies described no significant seizure reduction in any of the children [99]. Also a study in patients with previous resective epilepsy surgery showed a limited seizure suppressing effect of VNS [100] although another report described improved seizure control in this specific patient group [101]. A study of Sirven *et al.* included 45 patients who were 50 years of age and older. 31/45 patients had a follow-up of 1 year, with a reported responder rate of 68%, good tolerance and improvement of quality of life scores [102].

Safety, side effects and tolerability

Safety concerns with regard to VNS treatment can be approached from different angles. As the device needs to be implanted, a surgical intervention is required. The effects of delivering current to nervous tissue need to be considered as this might provoke changes in innervated organs and result into acute or chronic side effects. Patients with refractory epilepsy are often young people. The potential teratogenic effects of this new treatment have to be examined. The implanted device and wires have to be examined for MRI compatibility.

Perioperative side effects

The classical surgical technique has been described in detail by several authors [103–105]. Surgical techniques using a single cervical incision and sub-pectoral placement have also been described resulting in favourable cosmetic outcome in adults and children without prolonging the duration of the procedure [68, 106, 107]. Cosmetic side effects have also been improved since the production of the smaller Model 101 and will be greatly improved once the Model 103 Generator Demipulse and Model 104 Generator Demipulse Duo become widely available. Dimensions of the different VNS Therapy^{TM} are shown in Fig. 2. In the initial description of the implantation technique, Reid recommends general anaesthesia until the surgeon is comfortable with the approach [103]. The procedure should be carried out by a neurosurgeon familiar with the surgical approach for carotid endarterectomy because of the location of the vagus nerve in the neck in the carotid sheath between the carotid artery and the internal jugular vein. Surgical complications and difficulties are rare. Fluid accumulation at the generator site with or without associated infection occurs in 1–2% of patients and may respond to aspiration and antibiotics. Incisional infections are unusual and usually respond to oral antibiotic therapy and occur in 3–6% of the patients [6]. Rarely the generator or the electrodes have to be

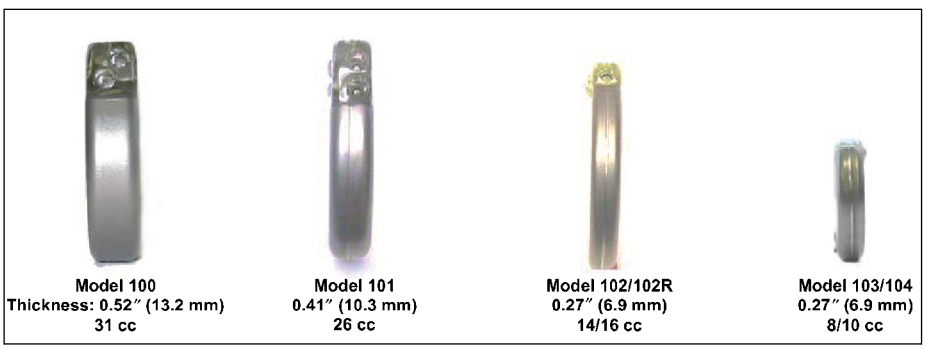

Fig. 2. Evolution in VNS Therapy pulse generators

removed. Some centers use prophylactic antibiotic treatment. This was done in the EO3 study and no infections were reported. In the EO5 study, infection led to device removal in 3/198 patients.

Patel *et al.* reviewed 11 cases of vagal nerve stimulator pocket infections in children. In all patients device removal was required to cure the infection [108]. Lower facial weakness is a side effect that was reported in 2 patients from EO3 and 2 from EO5 [56, 57]. It was attributed to high surgical incisions that are made to connect the electrode to the vagus nerve. With improvement of surgical techniques this side effect has not been reported since. Unilateral vocal cord paralysis occurred after approximately 1% of the implants in the controlled studies with full recovery after a few weeks in most cases. This may be due to intraoperative manipulation of the vagus nerve and subsequent damage to the vagal nerve vascularization [109]. One patient intended to enter the EO1 study, experienced a partial vocal cord paralysis due to nerve oedema [110]. This was considered a surgical complication as sutures, meant to aid at manipulating the helical electrodes, had been tied around the vagus nerve. Upon revision, the nerve was noted to have an oedematous aspect. Return to normal function occurred after removal. Left vocal cord paralysis occurred in 1 patient in the EO3 study and resolved when a malfunctioning device was removed. In two patients this complication was reported in the EO5 study. One recent study systematically evaluated vocal fold mobility in subjects before and after implantation. Thirteen patients underwent pre-implantation laryngeal electromyography and videolaryngoscopy. Two weeks after implantation and three months after implantation and activation of the device all subjects were revaluated. Perioperative vocal fold paresis occurred in approximately 50% of subjects [110].

Ramping up and long-term stimulation

For therapeutic purposes, VNS aims at stimulating vagal afferents. There are wide spread connections from the vagus nerve to the central nervous system. Through these connections efficacious stimulation parameters may also induce other central nervous system side effects. Moreover, selectively stimulating afferents is difficult and approximately 20% of the fibers in the cervical part of the vagus nerve are efferent fibers. These fibers innervate thoracoabdominal organs, which explains the potential serious side effects when these fibers are stimulated [111]. Certain side effects related to undesired stimulation of nerve fibers might be immediately perceptible by the patient. The main efferent innervation of the vagus nerve serves to monitor and modulate visceral activity. These autonomic processes are usually not perceived by the patient. There may also be side effects specifically related to chronic stimulation that will cause symptoms and become clinically apparent only after long-term treatment. The most prominent and consistent sensation in patients when the vagus nerve is stimulated for the first time, even at low output current levels, is a tingling

sensation in the throat and hoarseness of the voice. The tingling sensation may be due to secondary stimulation of the superior laryngeal nerve that branches off from the vagus nerve superior to the location of the implanted electrode but travels along the vagus nerve in the carotid sheath [112]. The superior laryngeal nerve carries sensory fibers to the laryngeal mucosa. Stimulation of the recurrent laryngeal nerve that branches off distally from the location of the electrode and carries motor (Aα) fibers to the laryngeal muscles causes the stimulation-related hoarseness [113, 114]. Fiberoptic laryngoscopy and video stroboscopic examination have shown left vocal cord adduction (tetanic contraction) during stimulation at 30 Hz or higher [114–118]. These stimulation related side effects are dose dependent which means that higher amplitudes, higher frequencies and wider pulse widths are associated with more intense sensations and voice changes [55]. With regard to side effects related to stimulation of vagal efferents, effect on heart rate and gastrointestinal digestion are of major concern. Stimulation of the efferent fibers may induce bradycardia and hypersecretion of gastric acid. The stimulation electrode is always implanted on the left vagus nerve, which is believed to contain fewer sinoatrial fibers than the right. It has been suggested that the electrode is implanted below the superior cardiac branch of the vagus nerve. In primates, including man, however, the most cranial efferents arise from the recurrent laryngeal branch of the vagus, which is distal to the electrode site and should consequently be activated by stimuli above their treshold [113, 119]. In the initial pilot trials and controlled randomised trials extensive internal investigations were performed, including continued monitoring in the long-term extension phases. With regard to potential central nervous system side effects related to stimulation of vagal afferents and their connections in the brainstem and cerebral hemispheres, some studies were performed to evaluate changes in EEG, sleep stages, balance and cognition. In most studies systematic AED plasma monitoring was performed. In the EO1 and EO2 studies there were no effects on heart rate after 3 months of stimulation as measured by electrocardiography (ECG) and Holter monitoring and no effects on gastric acid output as measured by fasting acid output during 1 h. There were no changes in the physical examinations, specifically systolic and diastolic blood pressure and body weight. There was no effect on AED serum levels [55]. EEG during sleep, anaesthesia and wakefulness was not affected [120]. Side effects reported by the patients in the EO1 and EO2 study were almost always related to the stimulation on-time and consisted of hoarseness and tingling sensation, left anterior neck muscle movement, hiccup, cough, shortness of breath during exercise [55]. Some of these side effects such as muscle movement may be due to collateral spread of current stimulating nervous structures in the vicinity of the vagus nerve [121]. Such events are often triggered by a certain posture e.g. head turning to the left or left lateral decubitus and may be relieved by changing position. In the EO3

study stimulation-related hoarseness was present in 1/3 of the patients, coughing and throat pain also gained statistical significance [111]. Hoarseness was significantly more present in the HIGH stimulation group. No cardiac or gastrointestinal side effects were present. Twenty-four-hour Holter monitoring in 28 patients (11 from the HIGH stimulation group, 17 from the LOW stimulation group) showed no VNS-related abnormalities [56]. One patient with mild hypercholesterolemia had a nonfatal myocardial infarction following 8 weeks of VNS. The relationship between this event and VNS is uncertain. In 14 patients, gastric acid output was measured showing a non-significantly increased basal gastric acid output during VNS that had no clinical correlate. There were no reports of gastric ulcers and no significant changes in pulse, respiration, blood pressure, temperature or weight [111]. Pulmonary function testing in a subgroup of 15 patients showed no influence of VNS on the forced expiratory volume after 3 and 9 months of stimulation [122]. In one patient with obstructive lung disease airflow obstruction occurred after increasing the stimulation parameters. Obstructive lung disease was considered a relative contraindication for VNS. Also patients with pre-existing obstructive sleep apnoea are at risk for increase of nightly apnoeas [123]. Reduction of stimulation frequency may prevent exacerbation of the condition. In the EO3 study, mean AED plasma concentrations during VNS were similar on monthly visits. In the EO5 study, a similar side effect profile was found [57]. One patient in the HIGH stimulation group had a compromised postictal respiration pattern, which led to device deactivation. In the extension phase, the device was restarted without problems. No other pulmonary function problems, as assessed by pulmonary function tests, were observed. Ninety-nine percent of patients completed the EO5 study indicating high tolerability for the treatment [57]. A notable increase of the perceived well-being during VNS treatment was found using a Global rating scale for quality of life scored by the patient, the investigator and a companion. In the patient series of 118 patients, 4 patients requested the stimulator to be turned off due to lack of efficacy. In none of the patients the device had to be turned off due to stimulation-related side effects. In the long-term extension trials, the most frequent side effects were hoarseness in 19% of patients and coughing in 5% of patients at 2 years follow-up; shortness of breath in 3% of patients at 3 years [60]. There was a clear trend towards diminishing side effects over the 3-year stimulation period. Ninety-eight percent of the symptoms were rated mild or moderate by the patients and the investigators [124]. Side effects can usually be resolved by decreasing stimulation parameters. Central nervous system side effects typically seen with AEDs were not reported. After 3 years of treatment, 72% of the patients were still on the treatment [60]. The most frequent reason for discontinuation was lack of efficacy. Holter monitoring in a sample of patients of the EO4 study showed no clinically symptomatic changes. Pulmonary function testing was performed

in 124 patients with no change between baseline and long-term treatment [59]. Initial studies on small patient groups treated for 6 months with VNS showed no negative effect on cognitive motor performance and balance [125–127]. These findings were confirmed in larger patient groups with a follow-up of 2 years [128, 129]. Hoppe *et al.* showed no changes in extensive neuropsychological testing in 36 patients treated for 6 months with VNS [130]. In patients treated for 3 months with VNS who underwent polysomnography and multiple sleep latency testing there was no change in sleep architecture and a marked decrease in daytime sleepiness was noticed [131]. After that, several studies investigated the effect of VNS on sleep and respiration and found no major respiratory changes [114], hypocapnia [59, 132], apneas [124, 133–136], a decrease in SaO_2 [137] and modification of the sleep structure [138]. A survey of 20 patients who responded to a questionnaire specifically addressing the issue of voice change showed that 95% of the patients experience some kind of voice change but that 100% would have a stimulator reimplanted knowing the vocal side effects they have [114]. Three studies investigated whether the effect on the vocal cord and laryngeal muscles influenced swallowing in the sense that orally ingested material could enter the subepiglottal larynx [71, 139, 140]. This could lead to aspiration and pneumonia. Using therapeutic VNS parameters there were no clinically significant swallowing problems. However, patients with severe mental and motor impairment, pre-existing dysphagia and benzodiazepine treatment might be at risk for swallowing problems during VNS on-time [71]. VNS can be interrupted during meals using the magnet feature although this was experienced as impractical by the parents of two patients on a long-term basis. One study investigated the effects of chronic VNS on visceral vagal function and found no significant adverse effect on gastrointestinal vagal function [141]. Despite the fact that the initial studies showed no clinical effect on heart rate, occurrence of bradycardia and ventricular asystole during intra-operative testing of the device (stimulation parameters: 1 mA, 20 Hz, 500 μs, ~17 s) have been reported in a few patients. None of the reported patients had a history of cardiac dysfunction, nor did they show abnormal cardiac testing after surgery. Tatum *et al.* reported on 4 patients who experienced ventricular asystole intraoperatively during device testing [142]. In 3 patients, the implantation procedure was aborted. In one patient a rechallenge of stimulation with incremental increases from 0.25 to 1 mA did not reveal a reappearance of bradycardia. Implantation was completed and no further cardiac events were noticed after start of VNS. Asconape *et al.* reported on a single patient who developed asystole during intra-operative device testing. After removal of the device, the patient recovered completely [121]. Ali *et al.* described 3 similar cases. Cardiac rhythm strips were available and showed a regular 'p'-wave (atrial rhythm) with no ventricular activity indicating a complete AV nodal block. In two of these patients the device was subsequently

removed. In one patient the device was left in place without experiencing any other adverse events after start of VNS [143]. Andriola *et al.* reported on 3 patients who experienced an aystole during intraoperative lead testing and who were subsequently chronically stimulated [144]. Ardesch *et al.* reported on 3 patients with intraoperative bradycardia and subsequent uneventfull stimulation [145]. Possible hypotheses with regard to the underlying cause are inadvertent placement of the electrode on one of the cervical branches of the vagus nerve or indirect stimulation of these branches, reversal of the polarities of the electrodes which would lead to primary stimulation of efferents in stead of afferents, indirect stimulation of cardiac branches, activation of afferent pathways affecting higher autonomic systems or of the parasympathetic pathway with an exaggerated effect on the atrioventricular node, technical malfunctioning of the device or idiosyncratic reactions. The contributing role of specific AEDs should be further investigated. Suggested steps to be taken in the operating room in case of bradycardia or asystole during generator and lead impedance testing have been formulated by Asconape *et al.* [121]. Adverse cardiac complications at start or during ramping-up of the stimulation intensity have not been observed [111]. Very recently, one case report described a late onset bradyarrhythmia after 2 years of vagus nerve stimulation [146].

Annegers *et al.* have reported on 25 deaths in 1819 patients treated with VNS. SUDEP rates were 4.1 in the VNS group versus 4.5 per 1000 for patients with refractory epilepsy. Within the VNS treated patients, SUDEP rates dropped from 5.5 per 1000 for the first 2 years of treatment to 1.7 per 1000 for the subsequent years suggesting a trend towards lower SUDEP rates in refractory epilepsy patients treated with VNS [147].

Table 3. *Suggested steps in case of intraoperative bradycardia and/or asystole [124]*

1.	Verfiy that electrodes are placed on the vagus nerve
2.	Locate the cervical branches to assure that electrodes are placed distally to their origin
3.	Verify device polarity
4.	Check that the leads are well seated into position and securely locked into the generator with the setscrews
5.	Check for saline or blood pool around the lead's stimulation coils
6.	Repeat stimulation at lower settings eg. 0.25 mA, 20 Hz, 250 μs, 14 s
7.	Use recorded ECG strip
8.	Proceed gradually to step up stimulation according to tolerance
9.	Consider using silastic dam to insulate against collateral stimulation of cardiac brances
10.	Defer starting prolonged VNS for two weeks after implantation to minimize collateral current spread

Miscellaneous side effects

In the literature there are several case reports on isolated adverse events [148–156]. A summary of these events is given in Table 4.

Psychiatric side effects have been reported by Blumer *et al.* who found an exacerbation of preexisting dysphoric disorders in patients with a >75% reduction in seizure frequency after treatment with VNS [157]. This 'forced normalization' appeared to occur more often when compared with AED treatment and can be successfully treated with antidepressant medication. It might also be related to the VNS-induced increase of alertness that is often reported and is unrelated to changes in seizure frequency. In patients with pre-existing psychiatric disorders decreased sedation and increased alertness may manifest itself as psychosis with hallucinations. Also De Herdt *et al.* reported on 4 cases of psychosis after VNS treatment [158]. In contrast to an increase in psychiatric disturbances, Koutroumanidis suspected a potential antipsychotic effect in patients with postictal psychosis. These symptoms disappeared in two patients who were treated with VNS following unsuccessful epilepsy surgery [100]. There are clear indications that VNS can interfere with psychiatric symptoms and that specific VNS-induced 'positive' side effects exist.

MRI/3 Tesla MRI

Most patients with refractory epilepsy who are treated with VNS have previously undergone MRI during the presurgical evaluation. It is not uncommon for such patients to require MRI after VNS implantation to further monitor underlying neurological diseases e.g. in case of unexplained increase in seizure frequency, follow-up of intracranial lesions and also for MRI indications as in the general population. Based on laboratory testing using a phantom to simulate a human body, the VNS Therapy^{TM} system device is labelled MRI compatible when used with a send and receive head coil [159]. In addition to the safety issues, there was no significant image distortion [160]. A retrospective analysis of 27 MRI scans performed in 25 patients at 12 different centers was performed in order to confirm the findings from the experimental set-up in a clinical series. All patients were scanned on a 1.5 Tesla machine. On one occasion a body coil was used. Three scans were performed with the stimulator in the on-mode. One patient reported a mild voice change for several minutes; one child reported chest pain and claustrophobia. Twenty-three patients reported no discomfort around the lead or the generator. It was concluded that MRI is safe as long as guidelines stated in the Physician's manual of the implanted device are followed. In these guidelines it is suggested to program the pulse generator output current to 0 mA. On one occasion this has led to the occurrence of a generalized status epilepticus in a patient who was well controlled with an output current of 2 mA. The authors of the report recom-

Table 4. *Miscellaneous side-effects*

Author	Side effect	Patients	Time of occurrence	Stimulation parameters	MOA
Kim *et al.* [148]	Horner syndrome	6 year-old	postoperative surgical continuous	unavailable	transient dysfunction of the oculosympathic fibers within the carotid sheath
Iriarte *et al.* [156]	episodic torticollis tonic contraction left SCM	20 year-old man	during stimulation on-time	30 Hz, 500 μs, 1 min on, 5 min off, 2 mA	electrical activation of motor fibers of SCM or of N. XI by proximity or antidromal through ramus internus or anatomic variant connecting N. X–XI
Sanossian and Haut [149]	chronic diarrhea	35-year old man	one week after VNS initiation	0.25–0.75mA, 30 Hz, 500 μs, 30 s on, 5 min off	idiosyncratic reaction in patient with pre-existing hemorrhoids or variability in number of vagal lefferents
Leijten and van Rijen [150]	dyspnoe and cabdominal discomfort in supine position with head turned to the left	42-year old man	several months after VNS initiation, during stimulation on-time in specific head position	2–2.25 mA, 30 Hz, 500 μs, 30 s on, 5 min off	leakage current coactivated the phrenic nerve that is approximated to the vagus nerve when head is turned to the left
Koutroumanidis *et al.* [151]	aggravation of epilepsy and appearance of a new seizure type	20-year old woman	4 months after VNS initiation, 2 days after output current increase	2.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off	breakdown of inhibitory mechanisms in specific functional and structural neuronal networks, facilitating discharge propagation

(*continued*)

Table 4 (*continued*)

Author	Side effect	Patients	Time of occurrence	Stimulation parameters	MOA
Gatzonis *et al.* [152]	pyschosis, schyophrenia-like syndrome	35-year old man	3 months after VNS initiation, at time seizure control was reached	1.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off	forced normalization
Kalkanis *et al.* [153]	self-inflicted delayed-onset vocal cord paralysis	20-year old woman with MR	15 days after surgery = VNS initiation	1 mA, 30 Hz, 500 μs, 30 s on, 5 min off	self-infliced injury to the vagus nerve from external manipulation of the device = 'Twiddler's syndrome' developmental disability: risk factor
		25-year old man with MR	6 days after surgery = VNS initiation	1 mA, 30 Hz, 500 μs, 30 s on, 5 min off	
Rauchenzauner *et al.* [154]	NT-proBNP levels increased during VNS and seizures	4-year old boy	One year after VNS implantation	2,5 mA, 30 Hz, 250 μs, 30 s on, 5 min off	Unspecific activation of the neuro-cardio-endocrine system
Guilfoyle *et al.* [155]	adjustment of a Strata valve shunt by magnet and subsequent underdrainage of CSF	14-year old girl	After 6 months of VNS	unavailable	Susceptibility of strata valves to strong magnetic fields

MOA Mechanism of action, *opthalm* ophtalmological *SCM* sternocleidomastoid, *N XI* 11th cranial nerve = acessory nerve, *N. X* 10th cranial nerve = vagus nerve, *SE* side effect, *RX* radiography, *CPS* complex partial seizure, *CSWSS* continuous spike waves during slow sleep, *MR* mental retardation.

mend that intravenous access should be obtained and a benzodiazepine should be either available or pre-administered in patients with a well defined response who are undergoing elective MRI and in whom the generator is acutely programmed to 0 mA. Functional MRI (fMRI) is a recently developed technique that allows non-invasive evaluation of cerebral functions such as finger movements and language [161]. It has been widely used for research but is currently increasingly applied to evaluate functional tissue in the neighbourhood of lesions before resective surgery and also for assessing language dominance in the presurgical evaluation of epilepsy patients [5, 162]. When fMRI in patients with VNS is used for research purposes to evaluate VNS-induced changes in cerebral blood flow, scanning should be performed in the on-mode. To prevent the device to be turned off during scanning, an adjustment in the surgical positioning of the device is necessary. The device should be positioned so that the electrode pins that are plugged into the generator are parallel instead of perpendicular to the long axis of the body [163]. There have been several studies in patients treated with VNS for epilepsy as well as for depression showing that fMRI is safe and feasible [164–167]. These studies were performed to elucidate the mechanism of action of VNS and will be discussed later in this study. The use of body coils may be indicated in patients requiring spinal MRI. When removal of electrodes is indicated e.g. due to insufficient efficacy, complete removal is recommended over cutting the distal edges and leaving the electrode in place [168]. Full removal of the electrodes allows potential future MRI with body coils. Heating of the electrodes is related to the lead length. If full removal of the electrodes is difficult the leads should be cut to less than 10 cm. In several of our patients uneventful MRI was performed according to the prescribed precautions. In one patient with frequent simple partial seizures successful and uneventful fMRI was performed with the stimulator in the off-mode.

Teratogenic effects of VNS

Teratogenic effects in the sense of deleterious effects on the development of an embryo or foetus seem unlikely due to an implanted device. One study investigated teratogenicy of VNS in rabbits [169]. There were no effect of VNS on any reproductive parameter including mating behaviour, number of matings required, viable and dead foetuses, litter size, individual kit weights and organ weights. Histological assessment did not reveal any changes or abnormalities in selected tissues including neural tissues. Pregnancy is a particular situation especially in women with epilepsy and even more so when the epilepsy is refractory. Women with refractory epilepsy are often treated with several antiepileptic treatments of which VNS may be one. There are no known AEDs/VNS interactions outside pregnancy so VNS-induced changes in AED blood levels with loss of seizure control seem unlikely. In 1998 Ben-Menachem

reports on 8 pregnancies in patients treated with VNS after retrospective analysis of ±1000 patients [170]. All patients were taking concomitant AEDs. Five pregnancies went full term resulting in unremarkable and healthy deliveries including one set of twins. Two elective abortions due to unplanned pregnancy and abnormal in utero foetal development respectively were performed. The abnormal development was attributed to AEDs. One patient reported spontaneous abortion although the actual pregnancy was never confirmed. It appears that VNS does not inhibit conception.

Discussion

Despite the fact that VNS is accepted in epilepsy centers worldwide as a valuable and reliable therapeutic option for patients who are unsuitable candidates for resective surgery, some specific issues remain to counteract its full therapeutic potential. From a clinical point of view, prospective randomized trials investigating long-term efficacy in comparison to other therapeutic options for patients with refractory epilepsy are still lacking. An ongoing multicenter randomized trial called PulSE is currently recruiting patients worldwide and may shed light on the exact position of VNS. Moreover in this trial, the so called 'positive side effects' of VNS are being investigated in a standardized way which may provide us with more objective data with regards to the effect of VNS on mood and quality of life. On the basis of currently available data the responder rate in patients treated with VNS is not substantially higher compared to recently marketed anti-epileptic drugs. Efforts to decrease the number of non-responders may increasingly justify implantation with a device. To increase efficacy, research towards the elucidation of the mechanism of action is crucial. In this way rational stimulation paradigms may be investigated. With a rapidly evolving biomedical world, various neurostimulation modalities will be applied in patients with refractory epilepsy. Future studies will have to show the precise position of VNS in comparison to treatment such as deep brain stimulation and transcranial magnetic stimulation.

Both from the clinical experience with VNS for epilepsy and other pathological conditions and from the research on the mechanism of action, interesting new ideas have arisen to increase clinical efficacy to explore the MOA and to identify different indications for VNS. Further elucidation of the mechanism of action of VNS may help to improve clinical efficacy. Animal research should be directed towards the identification of a useful model to evaluate the seizure suppressing effects of VNS. The initial experiments investigating VNS in the pentylenetetrazol and MES model prove difficult to be reproduced even in hands of experienced researchers. In Ghent University Hospital, VNS has shown efficacy in the motor cortex stimulation model. The seizure threshold in this animal model significantly increases following one hour of VNS. This

model can now be further applied to investigate the efficacy of different stimulation parameters. Apart from the acute seizure suppressing effects of VNS, the more chronic and estimated neuromodulatory effects should be further investigated in the laboratory. Investigating VNS in a chronic setting requires efforts to investigate animals in chronic conditions with specifically designed electrodes that allow long-term treatment. At Ghent University Hospital a chronic video-EEG monitoring unit with customised miniature vagus nerve electrodes has been designed for this purpose. Chronic epilepsy models that may be used are the genetic absence epilepsy model (GAERS). Despite the fact that absence seizures are generally benign and easily controlled with antiepileptic drugs, investigation of efficacy of VNS in the GAERS model may contribute to the identification of specific brain structures that are implicated in the MOA of VNS. Preliminary studies using the kindling model have been published. Ongoing work at Ghent University Hospital, is investigating the long-term effects of VNS in the rapid kindling model. The ultimate goal may be to investigate the efficacy of VNS in spontaneous seizures as observed in status epilepticus model or the kainate model. Hints towards involvement of specific neurotransmitters in VNS have been found. Further investigation of this topic may be performed using microdialysis techniques in different animal models.

With regards to research in humans, prospective studies such as the PulSe study may further elucidate the outcome of VNS as it is being used in a day to day clinical practice at the moment. Within the currently used VNS parameters many combinations are possible and the efficacy of different paradigms should be investigated in a prospective way to evaluate potential superiority of certain paradigms with regards to efficacy as well as battery life. A multicenter study between Ghent University Hospital, Dartmouth Hitchcock Medical center and Montevideo Neurological Hospital is currently investigating these issues. Because of the variability of different phenotypes of epilepsy, it seems simplistic to assume that there are specific combinations of stimulation parameters that will optimally benefit all different types of epilepsy and all refractory individuals. Individually guided stimulation parameter titration may be a more successful avenue. Research should therefore be directed towards finding non-invasive measures that can guide individual titration. Neurophysiological investigation such as evoked potentials and EEG recording especially would be very tempting tools. Interesting research lines include the investigation of VNS efficacy in specific epilepsy conditions and in other neurological conditions. Case reports on the efficacy of VNS in status epilepticus are encouraging and require further prospective studies in larger patients groups. From a more experimental view, VNS may be considered as part of a closed-loop system where triggered VNS is performed on a more indivualized basis. Research towards the development of transcutane-

ous systems may allow identifying predictive factors for response before chronic implantation is performed.

Conclusion

Patients with refractory epilepsy present a particular challenge to new therapies. VNS has demonstrated to be an efficacious and safe treatment. The current consensus on efficacy is that 1/3 of patients have a considerable improvement in seizure control with a reduction in seizure frequency of at least 50%, 1/3 of patients experience a worthwhile reduction of seizure frequency between 30 and 50%. In the remaining 1/3 of the patients there is little or no effect. VNS seems equally efficient for children. The degree of improvement in seizure control from VNS remains comparable to new antiepileptic drugs. Contrary to treatment with AEDs, efficacy has a tendency to improve with longer duration of treatment up to 18 months postoperatively. Analysis of larger patient groups and insight in the mode of action may help to identify patients with epileptic seizures or syndromes that respond better to VNS and guide the search for optimal stimulation parameters. Further improvement of clinical efficacy may result from this.

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Surgical anatomy and surgical approaches to the lateral ventricles

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With 37 Figures and 1 Table

Contents

Abstract

This study focuses on the surgical approaches to intraventricular tumors which have developed within the cavity of the lateral ventricle. The first section is dedicated to embryology and describes the wrapping of the telencephalic vesicles around the thalamus and the morphogenesis of basal nuclei and commissures. In the second section, the anatomy of the lateral ventricles is described, along with their arterial and venous vasculature, their relationship with the eloquent cortical areas and cortical sulci, and their relationship with white matter fascicles, especially the optic radiations. In the third part, the main surgical approaches to the frontal horn, to the ventricular atrium and to the temporal horn are detailed.

Keywords: Anatomy; surgical approach; lateral ventricle; tumor.

This study focuses on the surgery of intraventricular tumors which have developed within the cavity of the lateral ventricle. The authors have excluded:

- Tumors which arise from adjacent brain structures and then spread into the ventricles
- Tumors of the pineal area
- Trigonoseptal tumors extending to the frontal horn
- Tumors of the third ventricle growing into the lateral ventricles

Tumors of the lateral ventricle are rare, representing 0.8–16% of brain neoplasms. They affect young patients (average age is 40 years) and often present as benign lesions. They expand within an extensible cavity, leading to relatively minor disturbances despite their large size at the time of diagnosis [10, 15, 31].

Tumors of the lateral ventricle are particularly deep, overlaid by a cortical mantle which contains eloquent areas especially in the dominant hemisphere. The surgical approach is often difficult. The best treatment is surgery for most

of histological types, particularly when the tumor volume is large. In posterior locations, surgical routes threaten the optic radiations which overlay the lateral ventricle, leading to a postoperative lateral homonymous hemianopia in 10–30% of patients. The overall surgical mortality rate varies from 0 to 14%, related to vascular complications, arterial but mostly venous, and CSF circulatory complications [3, 8, 10, 31, 37, 45].

Every case requires thorough preoperative planning based on imaging to understand the site of origin of the tumor and origin of the vascular pedicles. Neuronavigation may be necessary to improve the approach. Progressive removal (debulking) of the tumor volume is essential when the route is narrow. An initial clipping of the feeding vessels can be justified for hypervascular tumors. It is also possible to use stereotactic radiosurgery especially for recurrent or small remnant tumors.

A – Embryology [11, 13, 22]

The lateral ventricles are the fluid-filled cavities of the telencephalic vesicles.

The anterior communication of the primitive neural tube or anterior neuropore (AN) closes during the 11th stade (embryo of 2.5 mm to 4.5 mm-24th day). The anterior vesicle forms the prosencephalon. At the 32nd day two lateral evaginations appear communicating by the anterior portion of the prosencephalon which becomes the median telencephalon, future anterior area of the third ventricle (V3) and interventricular foramina (IVF). The remaining prosencephalon becomes telencephalon.

Closure of the AN is made by the lamina terminalis (LT) – the future anterior wall of the V3 which is the diencephalic ventricle that includes the white commissures: optic chiasma, anterior commissure (AC), fornix and corpus callosum.

The telencephalic evagination wraps around the thalamus resting against the neurocranium during its morphogenesis. It develops forward (future frontal horn), then behind (future ventricular body), extends toward the posterior neurocranium and curves ventrally and laterally in the temporal fossa (temporal horn). The occipital expansion is a diverticulum of the LV.

The lower part of the wall of the telencephalic vesicles includes a large cellular proliferation which creates the striatum and future basal nuclei of the brain. Ependymal epithelium gives rise to neurones and glial cells which will migrate toward the surface to form the cerebral cortex.

The LT constitutes an important inductor. Few diencephalic or archipallidal commissures have a simple transverse orientation: posterior commissure and AC. Others will wrap around the thalamus either partially like the corpus callosum (CC) or entirely like the fornix (F) which will form the internal wall of the LV. The portion of medial cortex of the telencephalic vesicles located between the winding of the corpus callosum and the fornix will form the septum pellucidum (Spel) (Figs. 1 and 2).

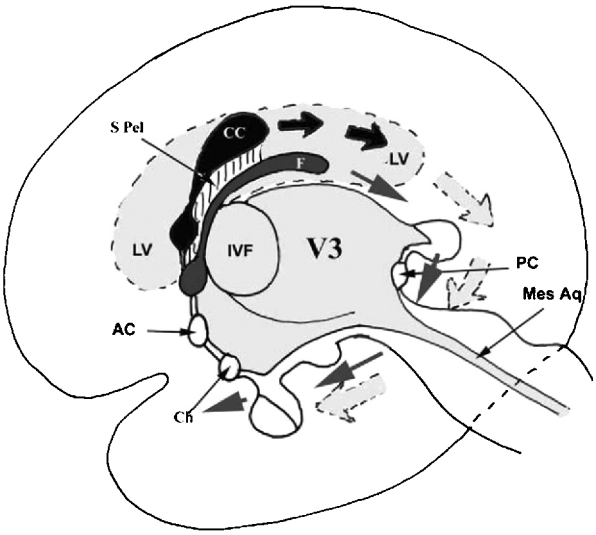


Fig. 1. Diencephalic winding on a medial sagittal section. Partial winding of the corpus callosum (black thick arrows). Complete winding of the fornix (thin black arrows) and of the LV (grey arrows). (PC: Posterior commissures; Mes Aq: Mesencephalic aqueduct)

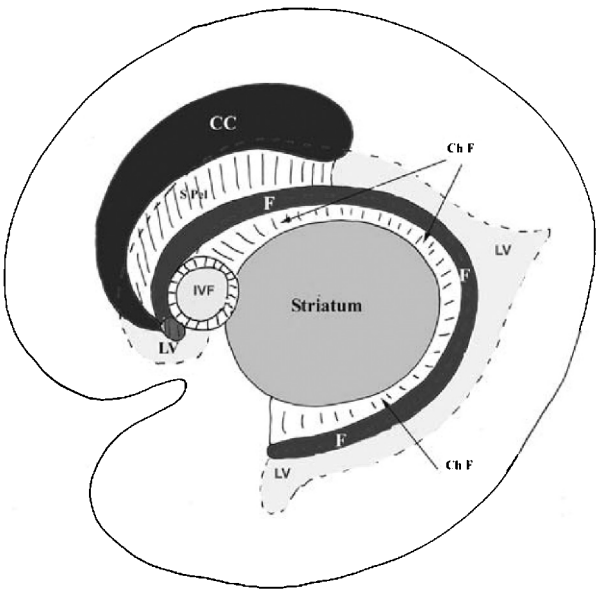


Fig. 2. Diencephalic winding and winding of the commissures (corpus callosum and fornix). Medial view of a telencephalic vesicle (ChF: choroidal fissure)

The LV behind the interventricular foramen (IVF) has a thick medial wall with an ependymal lining: it is the choroidal fissure (Ch F). This process is also completed during the development of the other ventricular cavities and con-

stitutes the membrana tectoria of the third ventricle and the fourth ventricle. The mesencephalic vesicle will keep the aspect of the primitive neural tube: its cavity will form the aqueduct of the mesencephalon (Mes Aq).

The leptomeningeal layer proliferates and gives rise to the choroidal plexus when it reaches the ependymal epithelium. The choroidal plexus develops into the choroidal fissure and extends in a C-shaped arc from the foramen of Monro through the body, atrium, and temporal horn avoiding the occipital diverticula (during the 18th–44th day).

The last fundamental embryological process is the fusion between the diencephalic vesicle and the two telencephalic vesicles which grow considerably and finally cover it (20th–51th day). The motor area of the diencephalon is directed laterally because of the prominent thalamus: the pallidum will merge with a part of the striatum (putamen) to give the lenticular nucleus which has a double embryological origin (Figs. 3 and 4). This nucleus does not wrap around the thalamus.

On the other hand, corticospinal pathways detaches a striate fragment which wraps laterally around the LV to form the caudate nucleus (CN).

The boundaries of the junction between the telencephalic vesicles and the diencephalons give rise to the transverse cerebral fissure (TCF) with two parts: one is horizontal with a horseshoe form opened ventrally toward the diencephalon-mesencephalon junction, the other is vertical directed ventrally and runs between the fornix and the roof of the third ventricle. The TCF concentrates the choroidal tela of the third ventricle and draws the superior boundary of the attachment. The venous ampulla courses in the ambiens cisterna. The pineal corpus forms the junction between the two parts of the FCT.

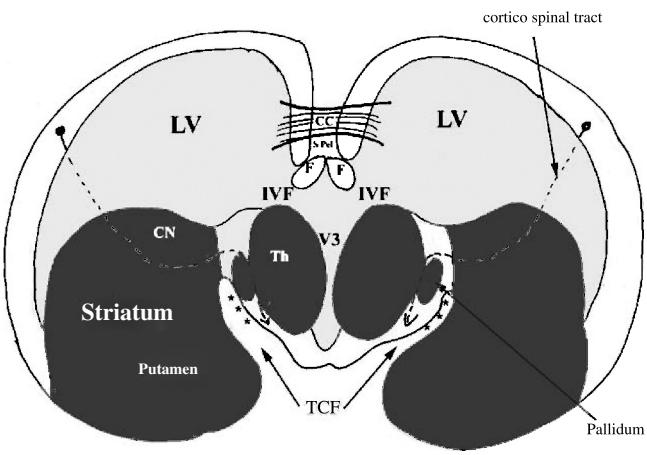


Fig. 3. Frontal section through the interventricular foramina before the joining between diencephalon and mesencephalon

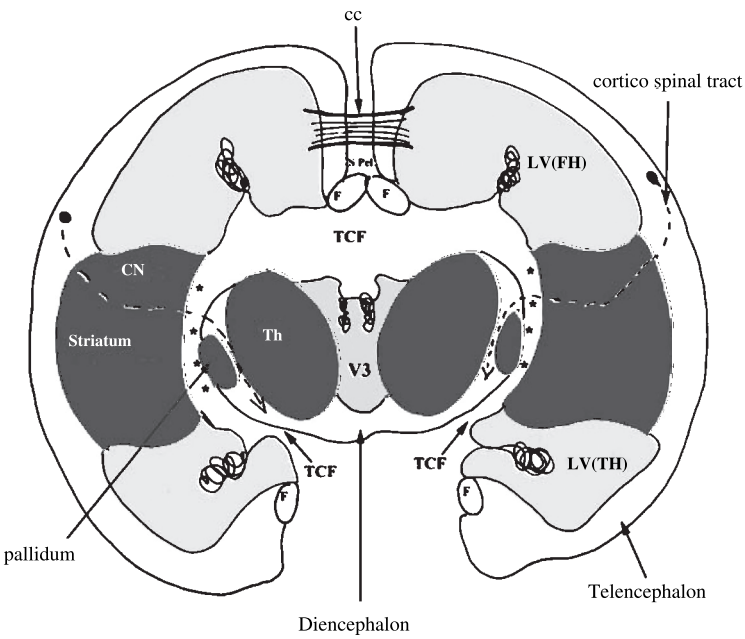


Fig. 4. Frontal section behind the interventricular foramina before the joining between the diencephalon and mesencephalon. LV(FH): lateral ventricle, frontal horn; LV(TH): lateral ventricle, temporal horn

B – Anatomy [1, 4, 5, 12, 19, 30, 34, 35, 38, 39, 40]

1. The cavity of the lateral ventricle (Figs. 5 and 6)

The lateral ventricles are two paired cavities deeply situated within each hemisphere. They have a horseshoe form as the result of embryological telencephalic winding. Each cavity contains about 10 cm^3 of cerebrospinal fluid and can be divided into:

- A frontal horn which has a ventral extremity in front of the interventricular foramen (IVF). Its length is approximately 6 cm
- A body between IVF and atrium
- A temporal horn or inferior horn or sphenoidal horn, whose length is 4 cm
- An atrium between these different parts

2. The walls of the lateral ventricle

2.1 The anterior frontal horn

The boundaries are:

– internal wall: septum pellucidum
– roof, anterior wall and floor: anterior wrapping of the corpus callosum, genu, rostrum and trunk

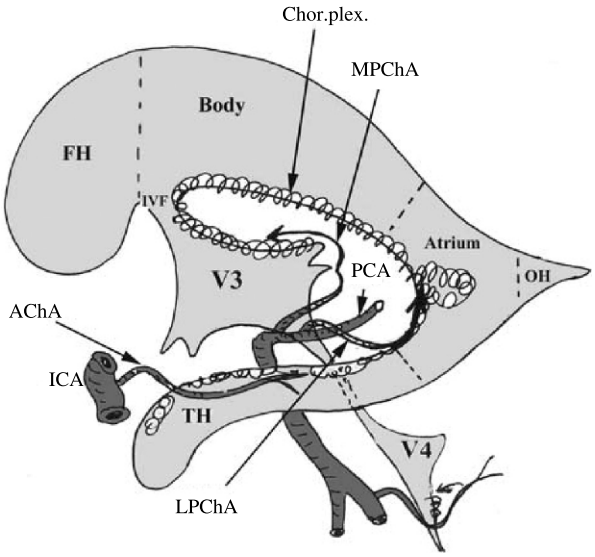


Fig. 5. Lateral view of the ventricular cavities and their vascular relationships. (Chor.Plex: choroidal plexuses-MPChA: medial posterior choroidal artery – PCA: posterior cerebral artery–AChA: anterior choroidal artery – LPChA: lateral posterior choroidal artery – ICA: internal carotid artery)

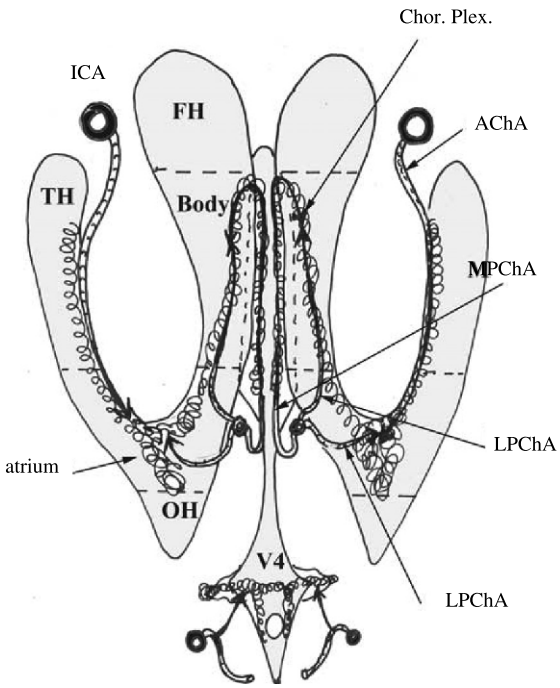


Fig. 6. Superior view of the lateral ventricular and arterial vasculature

– lateral wall: internal aspect of the head of the caudate nucleus.

2.2 The body of the frontal horn or central part of the LV (Fig. 7)

The boundaries are:

– internal wall: septum pellucidum and body of fornix
– roof: inferior aspect of the body of corpus callosum
– lateral wall: medial part of the body of the caudate nucleus
– floor: superoinferior aspect of thalamus between the thalamo-caudate sulcus and the tenia thalami (attach line of the choroidal plexus on the thalamus): this is the area of the lamina affixa. The thalamo-caudate sulcus contains the

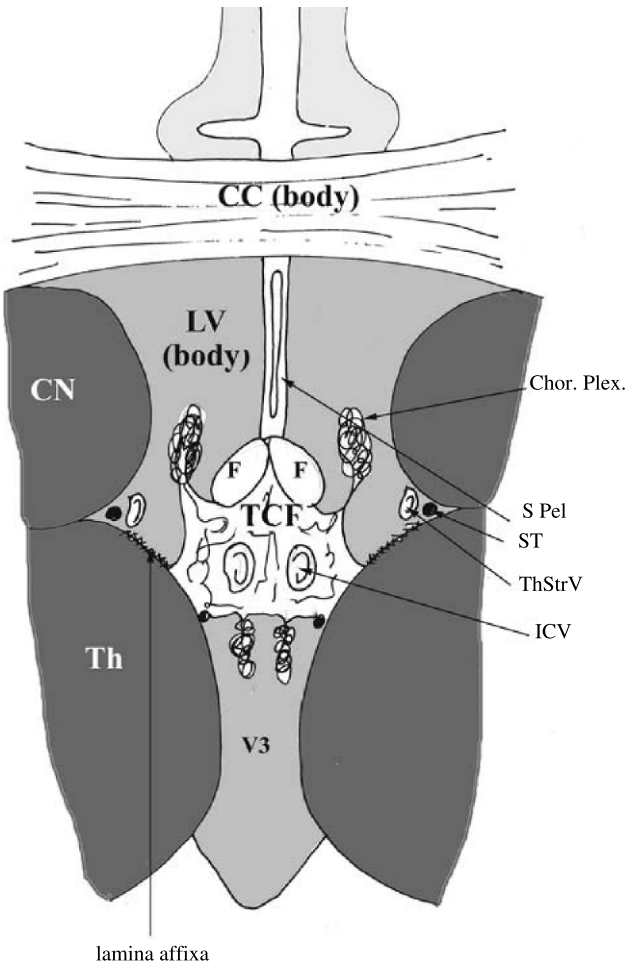


Fig. 7. Frontal section through the body of the LV

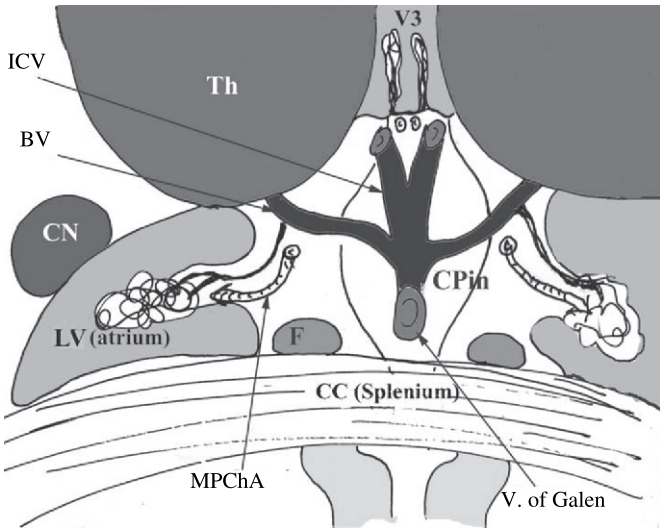


Fig. 8. Axial section of the atrium of the LV. (ICV: internal cerebral vein – BV: basal vein – CPin: pineal body)

stria terminalis (ST, white matter fasciculus connecting the amygdaloid nucleus with the hypothalamus and with the septal areas of the frontal cortex) and the thalamostriate vein (ThStrV).

2.3 The atrium (Fig. 8)

It communicates cranially, ventrally and medially with the frontal horn, dorsally with the occipital diverticle, and caudally, ventrally and laterally with the inferior horn. It overlies the pulvinar, posterior pole of the thalamus which constitutes the anterior wall. The fibers coming from the splenium constitute the roof. The choroidal fissura with the choroidal plexus (glomus) forms the medial wall and isolates the LV from the cisterna ambiens.

2.4 The occipital diverticulum (or occipital horn) (Fig. 9)

It extends towards the posterosuperior pole of the cerebral hemisphere. It does not concentrate choroid plexus. The walls are constituted by:

- internal wall: two prominences formed cranially and inferiorly by the fibers of the splenium of the corpus callosum (bulbar prominence) and the deep part of the calcarine sulcus (calcar alvis),
- floor: bulged by the collateral sulcus between T4 and T5 forming the collateral eminence,
- lateral wall: white matter of the tapetum formed by the external fibers of the splenium of the corpus callosum, overlaid laterally by the optic radiations (Opt.Rad) and then the inferior longitudinal fasciculus (Inf.Long.Fas.).

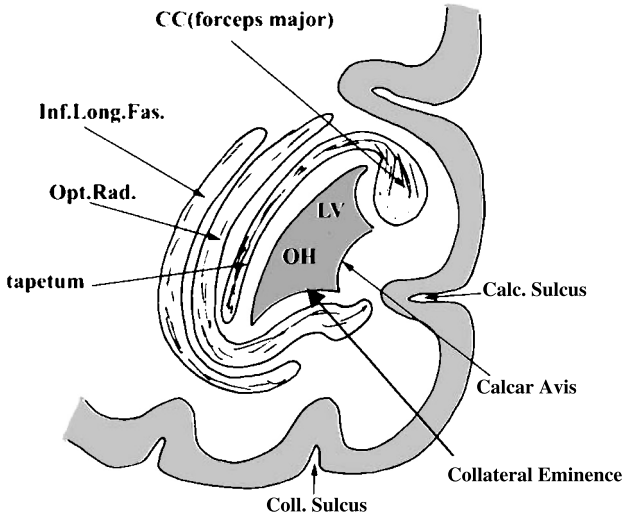


Fig. 9. Frontal section through the left occipital horn, anterior segment of the section (from Ebeling [12])

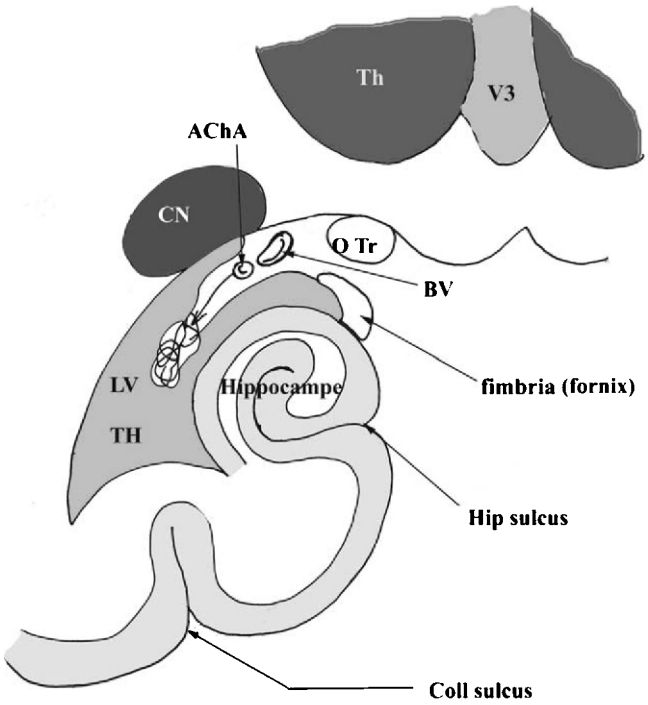


Fig. 10. Frontal section through the left temporal horn, anterior segment of the section (OTr: optic tract – BV: basal vein)

2.5 The temporal horn (Fig. 10)

It is formed by:

– floor: hippocampus or pes hippocampus and caudally the collateral eminence (prominence formed by the T4–T5 sulcus)
– roof: inferior aspect of the thalamus, tail of the caudate nucleus and deep white matter of the temporal lobe,
– internal wall: choroidal fissura and choroid plexus clinging to the fimbria which is the initial portion of the anterior crus fornicis and to the inferior aspect of the hemisphere.
– The anterior extremity is situated just behind the amygdaloid nucleus.

3. The interventricular foramen (Figs. 11 and 12)

The interventricular foramen is the communicating hole between the two LV's and the third ventricle. It is bounded on each side by the anterior pole of the thalamus and ventrally by the anterior crus fornicis. It has a diameter of 3–4 mm and presents a posterior concavity. It is marked by the reflexion of the choroidal plexus of the roof of the third ventricle which continues with the choroidal plexus of the LV and the venous angle between the thalamostriate vein and the internal cerebral vein.

4 Choroid plexus and CSF circulation

The choroid plexus is formed by the leptomeninx which leans on the ependymal epithelium bulging into the cavity of the LV at its medial portion through the choroidal fissura.

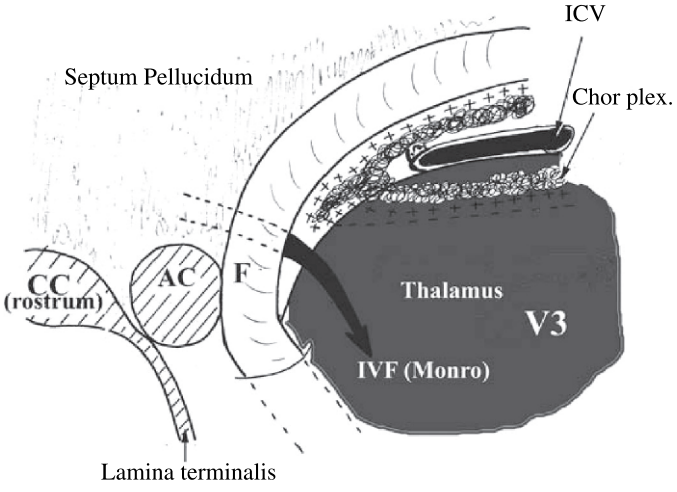


Fig. 11. Lateral view of the interventricular foramen (foramen of Monro)

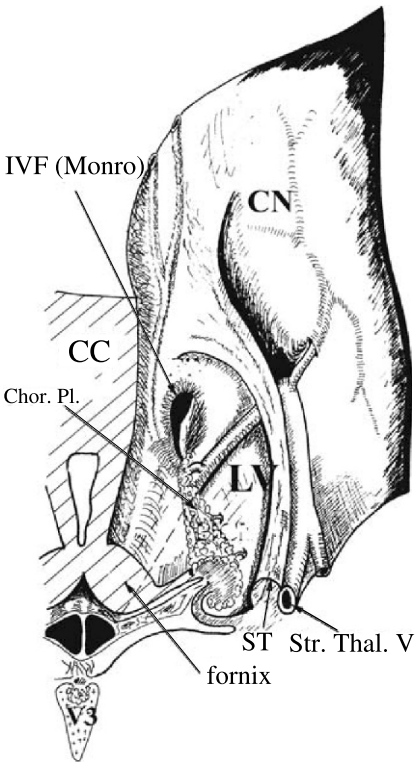


Fig. 12. Superior view through the frontal horn with the interventricular foramen (foramen of Monro)

The choroid plexus of the LV joins the choroidal plexus of the roof of the third ventricle through the interventricular foramen. It courses within the body, the atrium and the temporal horn. At level of the atrium, it is bulky and often presents with calcifications or cysts: it's the choroidal glomus.

The choroid veins mainly devious course over the choroid plexus and are well seen because they are bulky unlike the choroid arteries.

The CSF is secreted by the choroidal plexus with an active process via its main element the ependymal cell (blood-CSF barrier). This secretion is made in the LV with a circulation towards the IVF and the third ventricle. This can explain a possible cystic dilatation of a part of the LV (frequent at the level of the TH) caused by tumoral exclusion and disturbance of the CSF circulation.

5. Arterial vasculature of the VL (Figs. 1 and 13)

The choroid plexusi are supplied by choroidal arteries which have a small caliber and whose territory is not limited to plexusi but also includes telencephalic, diencephalic and mesencephalic adjacent nervous structures. Their number is vari-

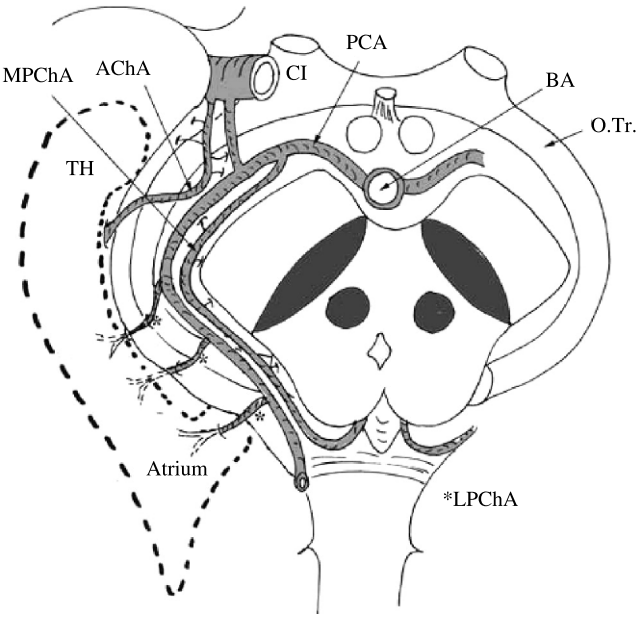


Fig. 13. Origin of the choroid arteries on an inferior view of the brain

able. They are deeply situated and reach the cavity of the VL on the medial face. They are hidden by the tumor and are not often exposed to the surgeon's sight.

5.1 Anterior choroid artery (AChA)

The AChA arises from the terminal segment of the internal carotid artery (C4) closer to the origin of the posterior communicating artery than the carotid bifurcation. The AchA has been reported to arise as a duplicate or double artery. It can divide quickly. Its origin is located on the posteromedial face of the internal carotid artery. It presents two segments: cisternal and plexal. The cisternal segment is concave laterally in a horizontal plan and concave rostrally in a sagittal plan; the plexal segment has a reversed course.

The cisternal segment (24 mm of average length) courses posteriorly below the optic tract. It encircles the lateral face of the cerebral peduncle. Then its course changes at the level of the lateral geniculate body to run through the choroidal fissure, reaching the superomedial part of the uncus to enter the anterior portion of the choroidal plexus within the temporal horn. The cisternal segment gives rise to its first large branch in the anterior portion of the temporal horn. It frequently anastomoses with branches of other choroidal arteries. The AChA sends branches (4 á 18) to adjacent nervous structures, and particularly the optic tract, the cerebral peduncle, the globus pallidus, the origin of the optic radiations. In approximately 50% of cases it sends a branch to the two posterior thirds of the internal capsule. This area of distribution is variable.

Moreover there is a balance between the territory of the AchA and the posterior communicating artery. Namely, their calibers often vary in the opposite direction.

5.2 Posterior choroid artery (PChA)

– The medial posterior choroid artery gives a few feeding vessels for the choroidal plexus of the VL except anterior anatomosis at the level of the interventricular foramen. It arises from the posterior cerebral artery posterior to the junction with the posterior communicating artery (P1 segment). It runs in the anterior portion of the cisterna of the transverse cerebral fissure and enters the ambiens cisterna to reach the choroidal tela of the third ventricle and its plexuses. Anastomoses are often found between the medial posterior choroidal artery and the lateral posterior choroidal artery (LPChA) through the interventricular foramen (IVF).
– The lateral posterior choroid artery (LPChA): their number per hemisphere ranges from 1 to 9 (average 4). It arises from either P2 segment or P3 segment of the PCA or from its branches. It runs laterally to the PCA and enters the choroidal fissura. The most important, arises from the P2 segment, sends branches to the glomus. Its area of distribution are the cerebral peduncle, fornix, pulvinar and caudate nucleus.

6. The veins of the lateral ventricles (Figs. 14–16)

These veins belong to the deep venous system of the brain and end in the internal cerebral veins (ICV) in the choroidal tela of the third ventricle and in the basal vein of Rosenthal which runs in the horizontal part of the transverse cerebral fissure with a circumpeduncular course where it sweeps over the PCA intersecting with the AChA.

– ***The choroidal veins*** are bulky and tortuous, easily seen, run over the plexus and only drain the plexus:
  - The superior choroid vein (12), very bulky, drains the glomus et runs ventrally towards the ventricle body to end close to the IVF either in the thalamostriate vein or in the ICV.
  - The inferior choroid vein (13) ends in the inferior ventricular veins and also in the basal vein at the same place.
  - The medial choroid veins course from the plexus of the ventricular body to the ICV.
– ***The veins of the ventricular walls*** drain not only the ependyma but also the adjacent parenchyma forming a deep venous territory draining the striatum, the internal capsule, the corpus callosum, the fornix and the septum pellucidum. There is a communication between the superficial venous system and the deep

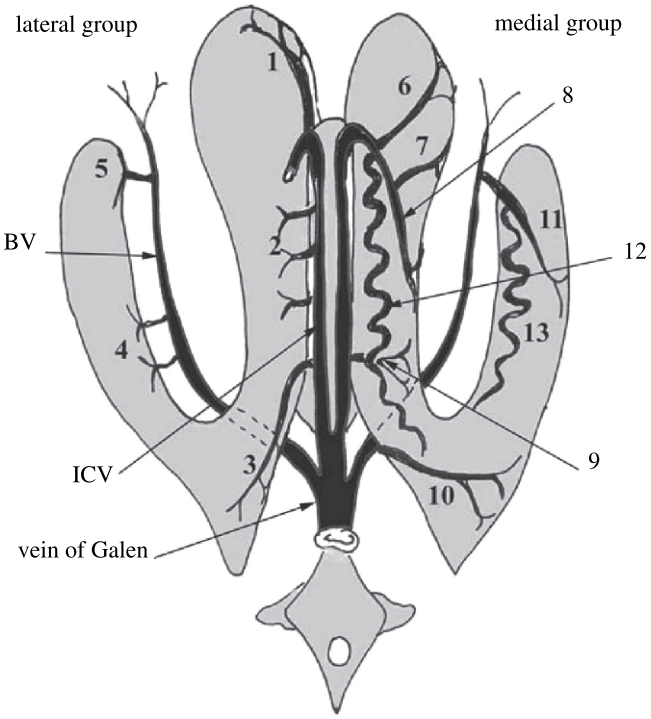


Fig. 14. Superior view of the ventricular veins

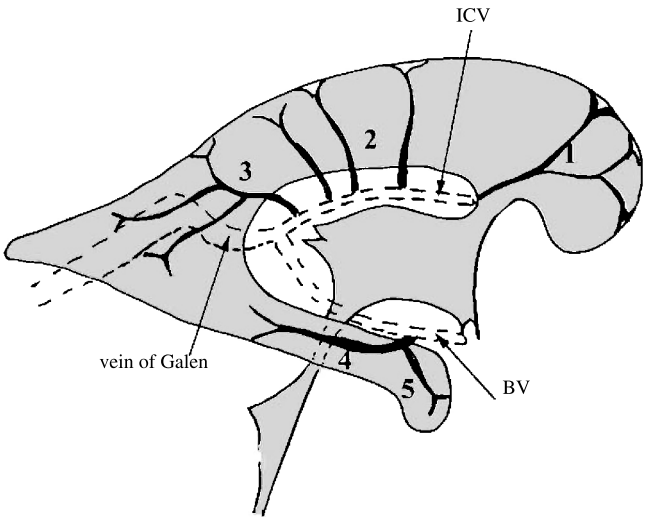


Fig. 15. Veins of the LV, medial group, lateral view

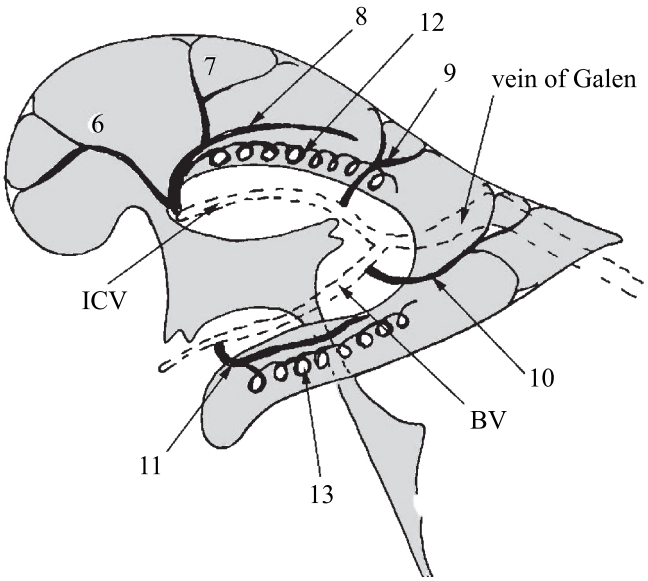


Fig. 16. ventricular veins, lateral group, lateral view

contrary to the arterial vasculature. However, these anatomoses do not protect the brain against venous infarction if they are sacrificed in approaching the LV. The ventricular veins can be divided into veins of the medial wall and veins of the lateral wall. They drain into the choroidal fissure.

- Veins of the medial wall of the LV:
  - Anterior septal vein (1), the most constant, drains into the venous confluent of the IVF.
  - Posterior septal veins (2) draining into the ICV.
  - Medial atrial veins (3) joining either the lateral atrial vein or the ICV or the medial occipital vein
  - Transversal veins of the hippocampus (4) draining into the basal vein or the ICV.
  - Vein of the amygdaloid body draining into the basal vein or into a transversal vein of the hippocampus.

- Veins of the lateral wall:
  - Anterior caudate veins (6), draining into the thalamostriate vein.
  - Thalamostriate vein (8), the most constant, runs in the thalamocaudate sulcus et forms the venous angle with the ICV through the IVF.
  - Posterior caudate veins (7) ending to the thalamostriate vein
  - Thalamocaudate vein (9) joins the ICV before the atrium. Its caliber is inversely proportional to the caliber of the thalamostriate vein.

– Lateral atrial veins (10) ending in the vein of Galien
– Inferior ventricular veins (11) in the CT converging in the basal veins.

7. Relationships of the lateral ventricles

They were mostly described in the section on the ventricular walls (corpus callosum for instance).

7.1 Cortical eloquent areas (Figs. 17 and 18)

Areas of comprehension of language (gyrus angularis, gyrus supra marginalis, middle temporal cortex and posterior cortex of the convexity) are close to the direct route to the ventricular atrium and hence a superior transparietal approach or a transcortical temporobasal incision are preferred.

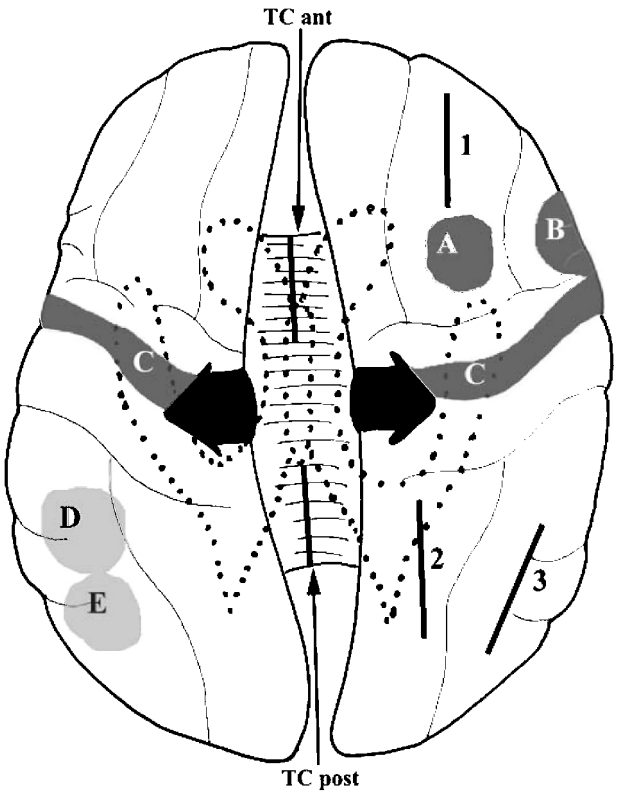


Fig. 17. Superior view of the cerebral hemisphere. (A, B, D, E: language cortical areas – C: motor cortex – 1: transfrontal transventricular approach – 2: posterior transparietal approach – 3: transparietal approach – TCant: anterior transcallosal approach – TCpost: posterior transcallosal approach)

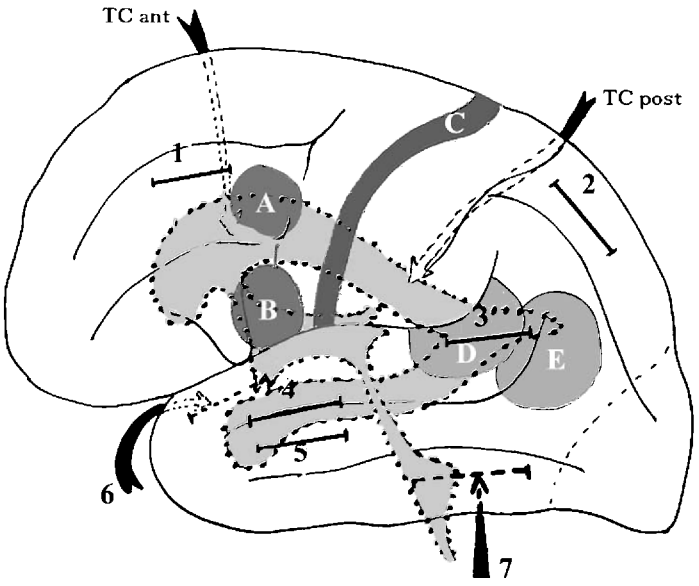


Fig. 18. Lateral view of the cerebral hemisphere. (A, B, D, E: speech cortical areas – C: motor cortex – 1: transfrontal transventricular approach – 2: posterior transparietal approach – 3: transparietal approach – 4: transsulcal T1T2 temporal approach – 5: T2 transcortical temporal approach – 6: transsylvian approach – 7: temporobasal or subtemporal transcortical approach – TCant: anterior transcallosal approach – TCpost: posterior transcallosal approach)

7.2 Distances between cortex and ventricular cavity (Fig. 19a and f)

The VL are deep structures which are developed on the medial face of the hemispheres at the diencephalomesencephalic junction. The CF and its cister-

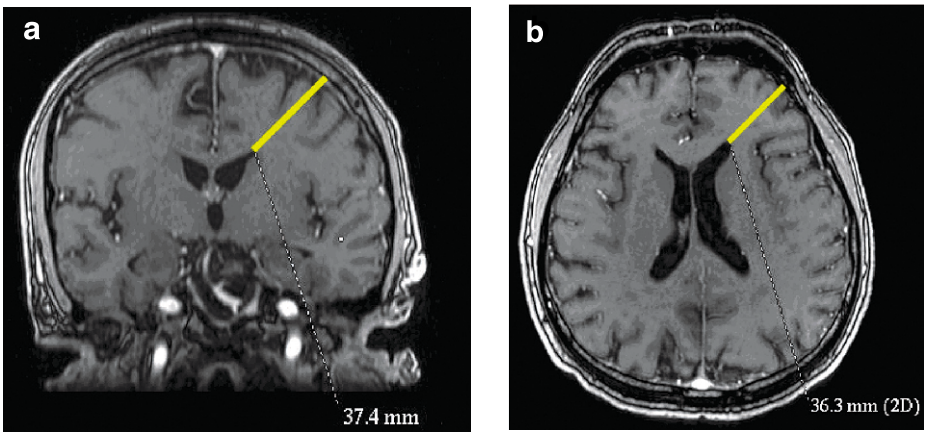


Fig. 19. (a, b) Distance between frontal cortex and frontal horn

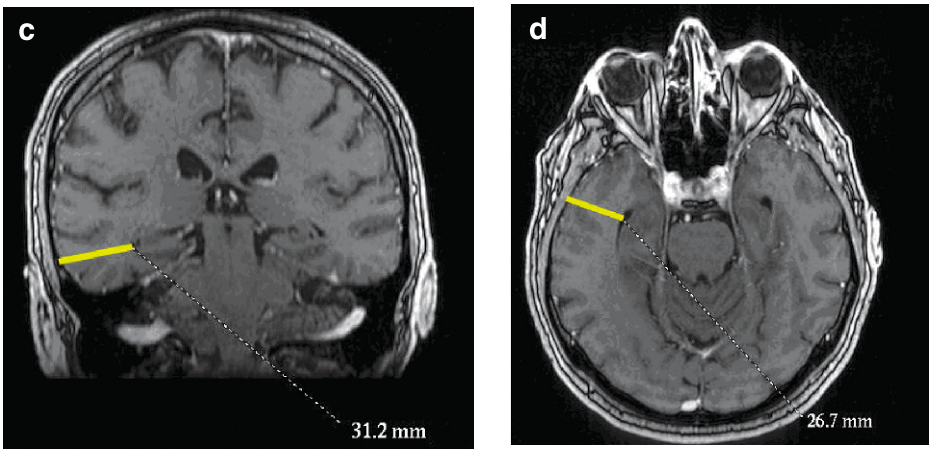


Fig. 19. (c, d) Distance between temporal cortex and temporal horn

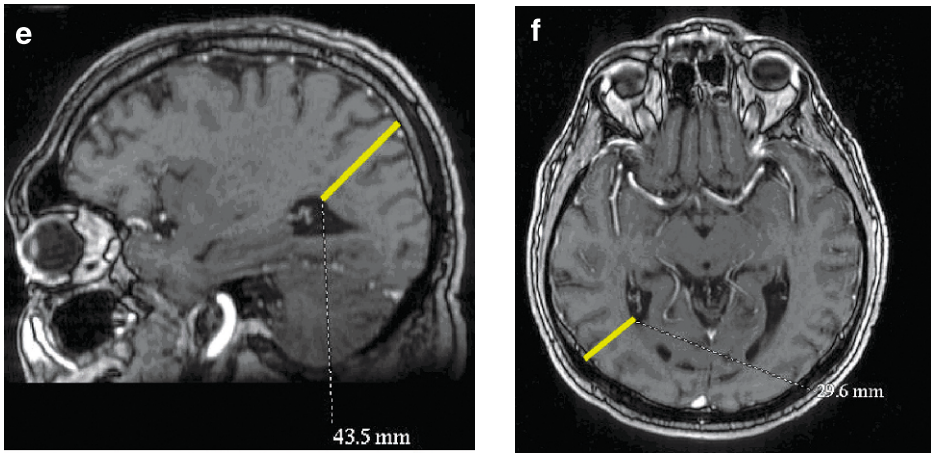


Fig. 19. (e, f) Distance between cortex and ventricular atrium

nal relationship, the transverse cerebral fissure, are the best anatomical landmarks. The neurosurgeon will prefer a route which is direct and straight but functional areas always play a decisive role for the final choice and will lead to changing the initial strategy.

Here are the average values from the literature:

- frontal cortex-IVF: maximum 60 mm
- frontal cortex – frontal horn: 35–40 mm
- temporal cortex – temporal horn: 25–30 mm
- cortex of the hemispheric cross-road – atrium: 30 mm
- parietal cortex – atrium: 50 mm
- occipital cortex – atrium: 55 mm

7.3 Relationships with the cortical sulci (Fig. 19g and h)

a – Anatomical relationships:
A few sulci bulge on the ventricular wall:

- *calcarine sulcus* forms the calcar alvis on the medial wall of the occipital horn.
- *Collateral sulcus* dividing the medial occipitotemporal sulcus (T5-O5, parahippocampal gyrus) and the lateral occipitotemporal sulcus (O4-T4, fusiformis gyrus) forms the collateral eminence on the floor of the temporal horn, of the atrium and of the occipital horn,
- *The hippocampal sulcus* raises on the medial wall of the temporal horn and forms the horn of Ammon.

b – Surgical relationships:
The sulci constitute a usable route reducing the length of the cortical passage and the brain injury. Microsurgical techniques reduce injury to the feeding vessels.

- *Longitudinal fissure of the brain* (interhemispheric fissure): it consitutes the transcallosal route, especially ventral. Only the corpus callosum which forms the roof must be incised. It reduces the cerebral lesions but does not reduce the distance to the frontal horn compared with the frontal F2 transcortical route. The bringing veins, sometimes the interhemispheric adherences, the presence of the anterior cerebral artery and its branches with interhemispheric anastomosis may provide challenges.
- *T1–T2 sulcus* is the deepest cortical sulcus, with the exception of the sulcus lateralis (scissure of Sylvius) and of the internal parietooccipital sulcus (in-

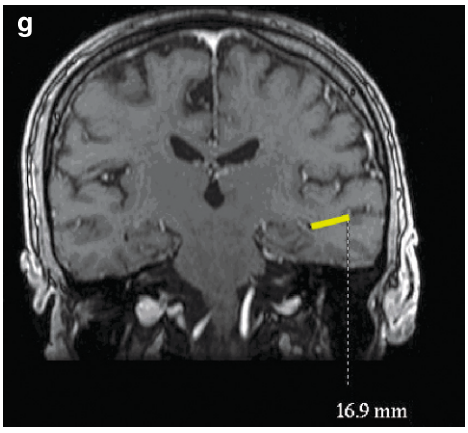


Fig. 19. (g) Distance between T1T2 sulcus and the temporal horn

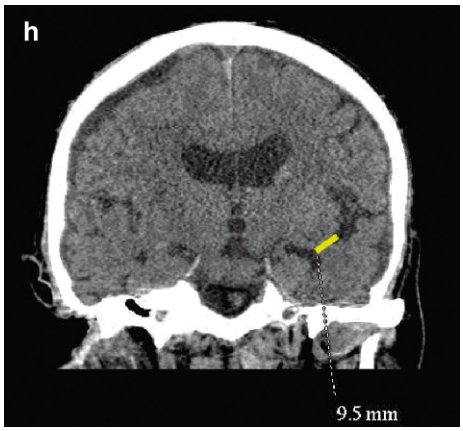


Fig. 19. (h) Distance between the sulcus lateralis and the temporal horn

ternal perpendicularis sulcus). It reduces by half the route to the temporal horn (Fig. 19g).

- *the sulcus lateralis* (scissure of Sylvius) reduces the route towards the temporal horn. Its opening allows passage through to the anterior and deep part of its temporal wall (Fig. 19h).

7.4 Relationships with white matter fascicles

These fascicles are crossed during VL approach. We can divide them into interhemispheric association fasciculi (or commissure), commissural fasciculi and projection fasciculi like for instance the optic radiations.

Some commissures (corpus callosum, fornix) have a known function whereas others have not. Nevertheless their surgical section is not insignificant. These fibers can be seen by diffusion tensor imaging (MRI tracking) (Fig. 20). This technique will provide tools for the planning of the operative trajectory, allowing a better understanding of the consequences of their surgical section.

a – Association fasciculi:

- The corpus callosum (Fig. 21)

The bulky interhemispheric commissure forms with its anterior part (rostrum and genu) the roof, the ventral extremity and the floor of the frontal horn of the LV. At the level of the ventricular body, the inferior face of the body of the corpus callosum forms the roof of the ventricular body. At the level of the atrium of the LV, the splenium of the corpus callosum breaks off the LV, separated by the crus fornicis. The fibers of the corpus callosum fan out in each hemisphere. The dense medial fibers bulge into the superomedial face of the occipital horn, above the calcar avis, prominence of the bulb. The thin lateral fibers fan out within the lateral wall of the occipital horn and form the tapetum.

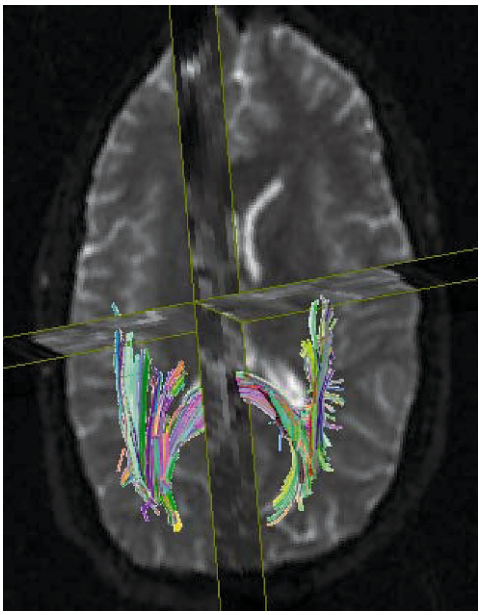


Fig. 20. Tracking of white matter fibers on MRI

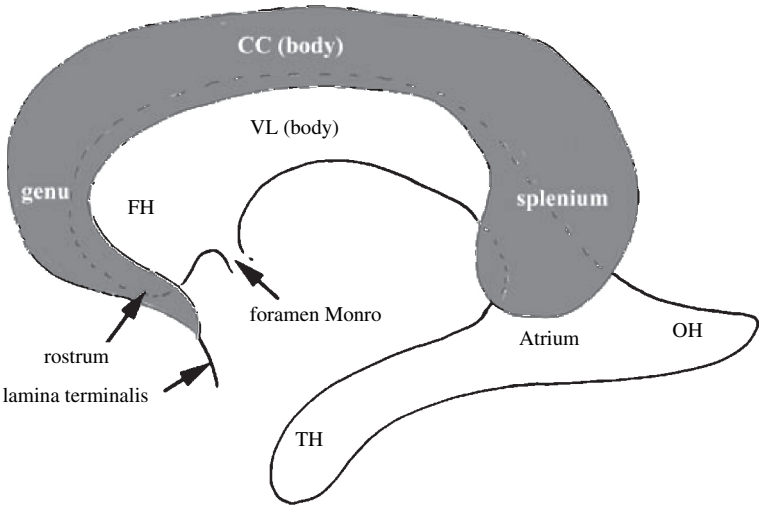


Fig. 21. Relationships of the corpus callosum with the cavity of the LV

- The fornix (Fig. 22)

It consitutes not only a projection fascicle from the hippocampal area to the mamillary body but also an association fascicle between two hippocampal segments thanks to the crus fornicis. From the hippocampus to the mamillary

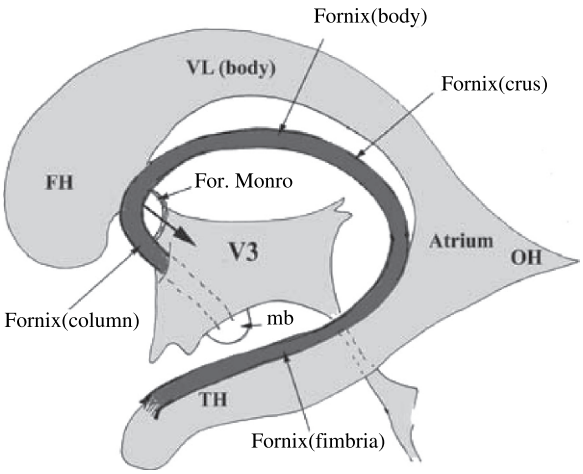


Fig. 22. Relationships of the fornix with the LV

body, it successively comprises the fimbria, the crura of fornix, the commissura, body and the columns which bound the IVF with the ventral pole of the thalamus. The fornix connects the choroidal structures (tenia fornicis) which run close to the choroidal incisura at the medial part of the temporal horn, of the atrium and of the floor of the ventricular body.

- Other intrahemispheric association fascicles:
  We will only detail the fascicles which are in the vicinity of the LV:
  - The subcallosal fascicle or superior longitudinal fascicle can be followed to the wall of the LV, where it connects the frontal lobe to the parietal, middle temporal and occipital lobes. This fascicle passes over the superolateral aspect of the caudate nucleus with a C-shaped arch.
  - Inferior occipitofrontal fasciculus interconnects the frontal lobe to the occipital lobe and courses superior to the optic radiations
  - Inferior longitudinal fasciculus connects the temporal pole to the occipital pole. It runs on the lateral wall of the temporal horn, of the atrium and of the occipital horn laterally to the optic radiations. It plays a role in visual memory.

b – Projection fascicles:

- Auditory radiations:
  These fibers arising from the medial geniculate body course toward the transverse temporal gyrus of Heschl and constitute a lateral relationship with the inferior horn, atrium, optic radiations and a portion of the anterior commissure. They belong to the retrolenticular area.

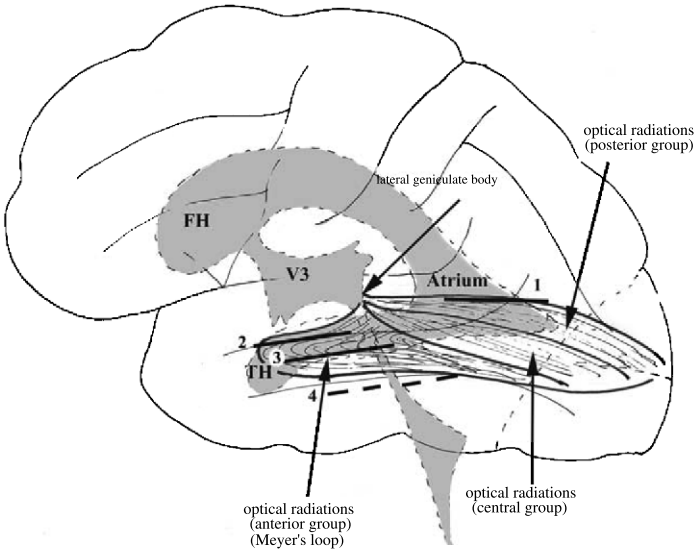


Fig. 23. Projection of the optic radiations on the wall of the LV. (1: parietal transcortical route – 2: T1T2 transsulcal temporal route – 3: temporal transcortical route – 4: temporobasal transcortical route)

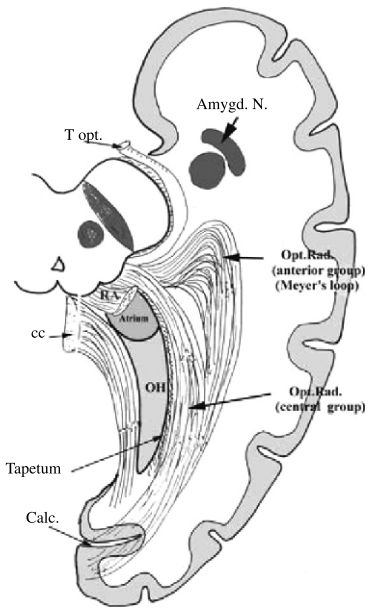


Fig. 24. Projection of the optic radiation on the wall of the LV. (Topt: optic tract – Amygd.N: amygdaloid nucleus – Opt.Rad.: optic radiations – RA: auditory radiations – CC: corpus callosum – OH: occipital horn – Calc: calcarine scissure)

- Optic radiations (Figs. 23 et 24):

They are the main relationship of the temporal horn, the atrium and the occipital horn of the LV. They arise from the deep face of the lateral geniculate body and reach the occipital cortex to join the upper and lower lips of the calcarine fissure. Campimetric deficit can be the objective signs of a tumor of the LV. Damage to these radiations is a major factor affecting surgical morbidity.

We divided the course of the optic radiations into three parts:

– the anterior group runs above the roof of the temporal horn and courses ventrally forming the Meyer loop which extends for an average distance of 27 mm behind the tip of the temporal lobe and up to 5 mm in front of the anterior extremity of the inferior horn. Then the fibers extend dorsally, in the vicinity of the lateral wall of the temporal horn, the atrium and the occipital horn and are the most ventral part of the optic radiations. They will end on the lower lip of the calcarine scissure (anterior part). They concentrate the fibers of the superior nasal homolateral visual field and superior temporal contralateral visual field. Their interruption will produce a lateral superior homonymous quadrantanopia on the opposite side of the lesion.
– the central group runs laterally, crosses the roof of the temporal horn and sweeps dorsally along the lateral wall of the atrium and the occipital horn. It is the most voluminous and concentrates the macular vision often preserved because of its bilateral projection. It ends on the two lips of the calcarine scissure occupying a great part of the primary visual cortex, dorsally to the peripheral visual field. Its damage will cause a lateral homonymous hemianopia on the opposite side of the lesion.
– the posterior group (or superior) passes directly behing the roof of the atrium to reach the superior lip of the calcarine scissure on its anterior part. It concentrates the fibers of the inferior nasal quadrant and inferior temporal contralateral of the peripheral visual field: its damage will produce a lateral inferior homonymous quadranopia on the opposite side of the lesion. It occupies the lower part of the optic radiations.

The optic radiations have a crescent shape at the level of the lateral wall of the temporal horn and atrium, and then horseshoe shape at the level of the occipital horn.

C – Surgical approaches

1. General considerations [15, 33–36, 42, 44]

Ventricular surgery requires working at depth, without the usual bone or vascular landmarks : the position of the patient must be simple and orthogonal. It is better to move the operative table or the operative microscope when the

ventricular cavity has been safely opened than to change the route or modify the operative field.

Magnetic resonance imaging and neuronavigation can be useful to avoid arterial and venous vascular pitfalls and to improve the entry point and the orientation to reach the intraventricular target. The benefit of neuronavigation disappears when the ventricular cavity is opened as brain shifts. Intraoperative MR may prove useful in the future.

The height of the ventricular cavity is essential for the surgical strategy:

- If a part of the ventricular cavity is dilated or excluded and easily approachable, its draining during the approach allows hemispheric sagging. It facilitates tumoral dissection, hemostasis of the ventricular walls and access to the tumoral vascular pedicle often located on the opposite side to the surgeon during the approach.
- If there is no ventricular dilatation, cerebral pressure makes tumor removal difficult. Cerebral shift can be helped by either an anaesthesetic protocol, or contralateral ventricular drainage placed under neuronavigation or also a lumbar drainage placed at the beginning of the operation and opened after the craniotomy. The distance between the cortical surface and the LV is often important. The use of a microscope with a long focal length is necessary. This operation may also require long surgical tools and cottonoids with a string to avoid their disappearance within the ventricular cavity outside the operative field of the neurosurgeon.

Cerebral retractors must be used with caution. Pressure over 30 mmHg for more than 30 min reduces local cerebral blood flow by 80% with pressure over 50 mmHg local cerebral blood flow becomes non-existent. Excessive brain retraction may create venous infarcts especially where venous sacrifice have been necessary. The use of a retractor should only be temporary during a deep approach. It is preferable to modify either the pitch of the table or the operative microscope to expose correctly an anatomical area than to increase retraction of the brain.

In these difficult anatomical areas, it is preferable to debulk the tumor and to reduce tumoral volume before dissecting the walls to obtain a complete removal. A balance must be struck between complete removal and damage to periventricular structures given that most of these lesions are benign.

Surgery of the LV must respect the ependyma and the veins of the ventricular walls whose fragility leads to difficulties with hemostasis, dissection and exposure. The most perfect haemostasis does not always release obstructed CSF flow. Fenestration of the septum pellucidum is usually made and it is preferable to leave a CSF external drain postoperatively. This drainage can be left closed according to the quality of intraventricular haemostasis at the end of surgery. This procedure avoids potentially dangerous acute postopoerative hydrocephalus.

2. Tumors of the frontal horn

2.1 The transfrontal transventricular approach [3, 21, 24] (Figs. 25, 26, 34)

- Position

The patient is placed on the operating table in a supine position, the head straight and a little flexed (10°). Other authors state a preference for a head which is rotated by 30° toward the opposite side. We think that it is preferable to identify the deep anatomy when the head is straight.

- Scalp incision

The scalp incision can be a frontoparietal arc passing over the coronal suture (2 cm behind), at the level of the middle line medially and passing ventrally 5–6 cm in front of the coronal suture. Other authors prefer an incision parallel to the coronal suture passing 2 cm behind it extending from a preauricular and susauricular region to the other. Moreover this incision exposes the bone landmarks (coronal and sagittal sutures) and allows placement of the craniotomy at the correct place. It is preferable to avoid any bald areas and to pass far from the craniotomy. The shaving is limited to the scalp incision, but also enlarged behind the craniotomy to allow exit of the ventricular drainage in an aseptic area.

- The size of the craniotomy

The bone flap is rectangular, frontoparietal and placed close to the mid-line. A burr hole tangential to the midline is placed immediately behind the bregma. It is not helpful to expose the cortex dorsally to minimize any risks to the motor area. A second burr-hole is placed also tangential to the midline about 4–6 cm in front of the first burr hole. One to two burr holes on the vertex are sometimes necessary in accordance with the age of the patient and with the adherence of the dura, 4–6 cm laterally to the midline. Separation of the dura from the midline must be prudent avoiding damage to the superior sagittal sinus.

The transventricular transfrontal route does not require exposure of the midline. It is not necessary to expose either the superior sagittal sinus or its lateral side: a craniotomy performed 1 cm from the anatomical midline is sufficient.

After the opening of the dura, dural hitch stitches are tightened because of the cortical collapse, which is very important at the end of the procedure and related to ventricular drainage.

- Dural opening

Incision of the dura parallel to the sides of the craniotomy is used. It should be performed in the external third of the craniotomy and extended towards the midline under direct vision to avoid damage to frontal bridging veins which sometimes run in the thickness of the dura. The reflection and suspension of

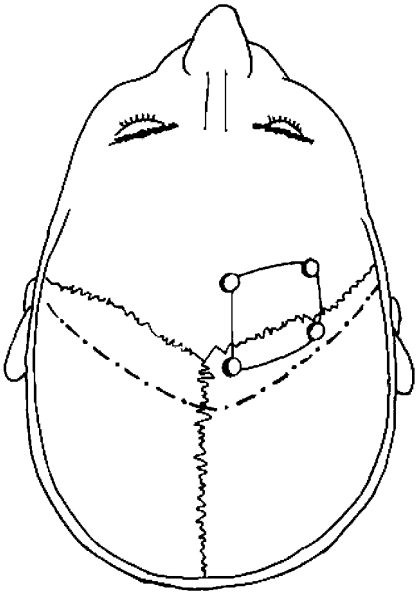


Fig. 25. Transfrontal transventricular route: scalp incision and craniotomy

the dural flap must be carefully inspected to avoid stretching of the cortical dural veins and decrease of sinus calibre by an excessive traction.

- Cortical incision

If the cortex is very tight, a ventricular puncture can be performed with a Cushing trochar towards the frontal horn of the LV. The introduction of the trochar can be made in the middle part of the frontal middle gyrus.

Otherwise, a cortical incision is performed parallel to the orientation of the frontal cortical sulci. It is placed in the middle of the middle frontal gyrus and measures 2 to 3 cm in length. After the cortical incision, splitting of the white matter towards the LV is relatively avascular. It can be very easy if the LV is dilated. The orientation of this dissection is performed towards the IVF, with the following landmarks:

– In a frontal plane, a line connecting the corticotomy and the internal canthus of the opposite side
– In a sagittal plan, a line joining a point placed 1 cm in front of the coronal suture and external ear.

The approach towards the LV must keep its length during incision of the white matter to avoid surgery through a funnel. When there is significant hydrocephalus, the surgeon must anticipate the shift of the brain in relation to the ventricular opening. The initial cortical incision should be placed more ventral than posterior.

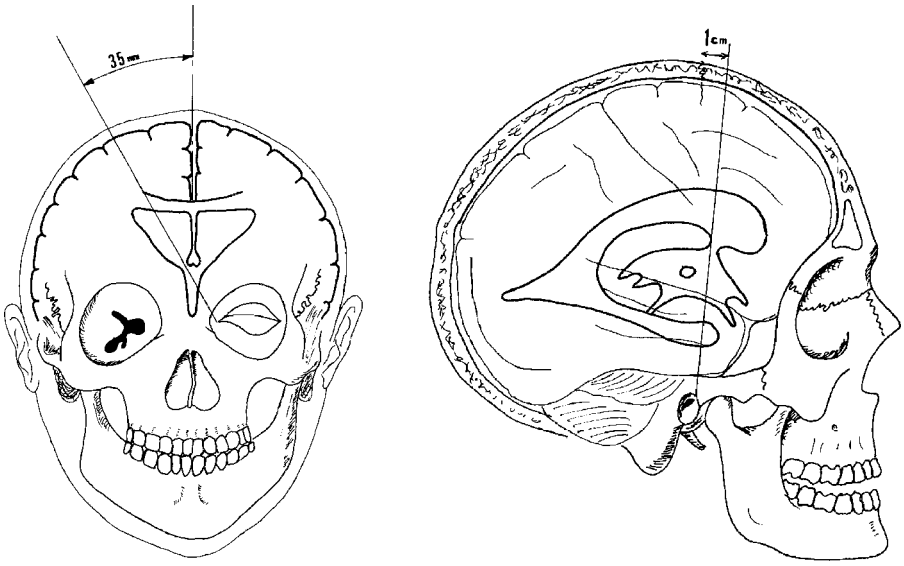


Fig. 26. Transventricular transfrontal approach: access to the LV

Other authors prefer that a glove finger around a Cushing trochar be introduced into the frontal horn of the LV. The swelling of this glove finger with a physiological fluid can dilate the route without cutting the frontal fibers.

The exposure of the cavity of the LV is oblique, oriented from cranial to caudal and from lateral to medial, centred on the IVF. We can imagine an incision through the superior frontal gyrus rather than through the middle frontal gyrus to obtain an optimal vertical trajectory. But this route seems to be illusory. An incision through the superior frontal gyrus risks damage to the bridging veins of the superior sagittal sinus and can intersect vessels of the cingulate sulcus. Moreover, the angulation obtained will never be as vertical as an interhemispheric transcallosal route.

- The entry into the LV results in cortical collapse due to CSF drainage. The walls of the corticotomy are carefully controlled with tamponade using cotton and surgical hemostatic agents such as Surgicel. Exploration of the field is performed with two retractors of 20–25 mm in width. They must be placed without excessive traction. Care must be taken not to obstruct the introduction of instruments in the operative field.

If there is a major ventricular dilatation, the septum pellucidum can bulge into the opened ventricle and hide the IVF. The septum pellucidum can then be opened in its middle portion cranially and dorsally to avoid damage to the fornix. The collapse of the contralateral ventricle restores the septum to the midline and restores the position of the fornix to expose the IVF.

The most frequent complications following transfrontal transventricular approach are transient mutism (11% of patients), epilepsy (26% of patients), hemiparesis (7% of patients), and short-term memory disturbances [3].

2.2 The anterior trancallosal approach [2, 7, 16, 17, 19, 23, 32, 34–36, 43, 45] (Figs. 27, 28, 35)

- Position and scalp incision

The position of the scalp incision can be similar to the transventricular transfrontal approach. Nevertheless, the transcallosal route is chosen particularly when there is no ventricular distension. If there is no obstacle to the pathways of the CSF, a lumbar drainage can facilitate the cortical collapse and access to the interhemispheric fissure.

- The size of the craniotomy

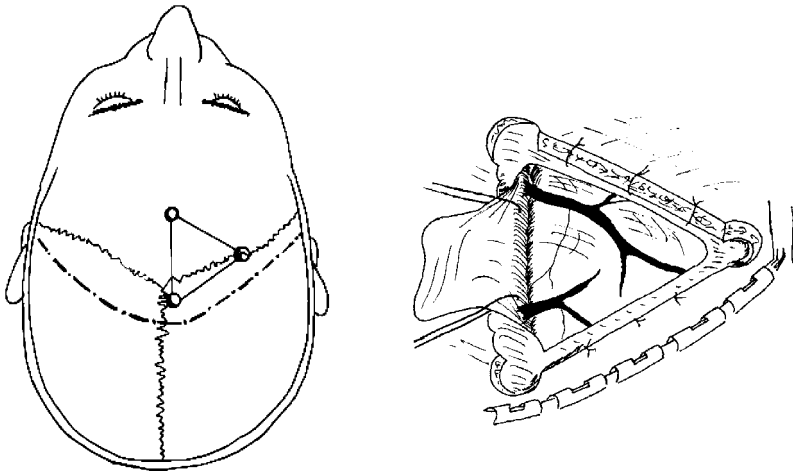
The craniotomy is similar to the craniotomy used for the transventricular transfrontal approach but can be smaller, particularly laterally where it is not necessary to expose so much frontal cortex. A first burr-hole tangential to the midline is placed immediately behind the bregma. A second burr-hole is also placed tangential to the midline, 5 to 6 cm in front of the precedent. Laterally only one burr-hole is required to perform a triangular shaped craniotomy.

Thorough analysis of the MRI allows anticipation of any difficulties with adjustment of the operative craniotomy. If there are many veins of large calibre, the risk of a venous sacrifice increases backwards towards the central (rolandic) area. This risk also increases with the extent and duration of the cerebral retraction.

The midline must be exposed. Care must be taken to separate the dura along the midline to avoid damage to the superior sagittal sinus. The use of a Gigli saw allows the craniotomy cut to be bevelled without risk to the venous sinus and to trim securely the internal table with an up cutting punch to expose the superior sagittal sinus. Care must be taken to respect the external table above the sinus and to avoid a deformation of the internal dural flap which can threaten the sinus during the procedure. Before the dura opening, dural hitch stiches are placed as there is cortical collapse at the end of surgery related to the ventricular drainage.

- Dural opening

The dural incision starts in the external third of the craniotomy with extension towards the midline performed under direct vision to evaluate the number and course of the bridging veins. Dural incision must be performed up to the corner of the superior sagittal sinus to expose perfectly the falx. If the craniotomy is correctly placed, the mooring veins do not inconvenience this exposure. If several



Figs. 27 and 28. Anterior transcallosal approach: scalp incision, craniotomy and dura opening

intradural veins prevent exposure of the falx, it is necessary to sacrify one. It is preferable to choose the more anterior veins because of their small caliber.

If the cerebral cortex does not relax despite lumbar drainage, or if this drainage has not been used, puncture of the frontal horn with a Cushing trochar can provide cerebral relaxation.

- Dissection of the interhemispheric scissure

This must be performed under operative microscope. The first stage consists in choosing the site of retraction of the frontal internal cortex to reach directly the IVF. More precise landmarks can be given by neuronavigation. When there is no neuronavigation, in a sagittal plane, a line between the coronal suture and the external auditory meatus (which can be palpated under the operative field) passes by the IVF.

After the use of a retractor along the medial face of the hemisphere, the dissection continues vertically along the falx. Small veins joining the medial hemispheric face to venous lakes are sometimes present: their interruption causes no problem because the flux of the medial venous drainage is centripetal. The depth of the falx increases dorsally and can be partially dehiscent. Opposite to the dehiscences or below the inferior wall of the falx, the dissection is more difficult because of an arachnoidal symphysis of the internal face of both frontal lobes. The dissection is sometimes possible whilst remaining in the arachnoidal plane. The medial faces of the two frontal lobes underneath the falx may also be very closely glued together or interdigitate and it is frequently impossible to nicely and cleanly separate the two pial layers [2].

The first artery encountered during the dissection may be the callosomarginal artery which runs above the cingulate gyrus. It may be confused with the

pericallosal artery but the cingulate gyrus has not the usual white pearly color of the corpus callosum. 5 cm in front of the coronal suture, the sulcus cingularis is placed on average 25.7 mm below the superior side of the hemisphere. The real pericallosal artery will be identified later during the dissection. It runs in the callosal sulcus, sometimes hidden by the relief of the cingulate gyrus. We should keep in mind during the procedure the anatomical (number and course) variations of these pericallosal arteries. When the pericallosal arteries are exposed, the best solution is to separate them softly to perform an incision through the corpus callosum between them: this procedure spares the perforating branches which arise from their external and inferior side, and which course towards the corpus callosum itself and the internal face of the cerebral hemispheres. Some surgeons protect these arteries with patties socked in papavenine.

When the ventricular cavities are dilated, the pericallosal arteries may be invisible and hidden in the sulcus cingularis below cingulate gyrus. Care must be taken not to dissect them if the superior face of the corpus callosum is correctly exposed for the continuation of the operative procedure.

- Incision of the corpus callosum

This is performed between both pericallosal arteries in a longitudinal directionand has a length of 2 to 3 cm. The corpus callosum is avascular and its thickness varies between 6 to 7 mm. Once the corpus callosum is incised, the CSF flow emerging from the ventricular cavities relaxes the hemisphere. The hemispheric retractor is placed over cottonoids to protect the cortex. Its tip must raise the incised side of the corpus callosum. The retractor on the midline, against the falx, must be placed meticulously to avoid compression of the superior sagittal sinus.

As the corpus callosum is incised, recognition of the anatomical landmarks is essential to continue the procedure (Fig. 28).

– If the transcallosal approach leads to the ipsilateral LV, the anatomy of the IVF is exposed as planned and is recognized.
– If the anatomical landmarks (choroid plexus and thalamostriate vein) are visible but with inverse relationships, the transcallosal route has lead into the contralateral LV. This situation is not unusual for a right-handed surgeon. The septum pellucidum can be incised to obtain confirmation. The incision of the septum pellucidum is sometimes necessary as the transcallosal approach visualizes the homolateral LV because the septum pellucidum can bulge into the LV and obstrue the IVF when there is a hydrocephalus.
– If the transcallosal approach leads into a ventricular cavity without veins or choroid plexus, it may indicate a cavum septi pellucidi. This should have been anticipated from the pre-operative MRI.

The anterior transcallosal approach can be complicated by transient mutism (18% of patients), visual and verbal disconnection syndrome which tends

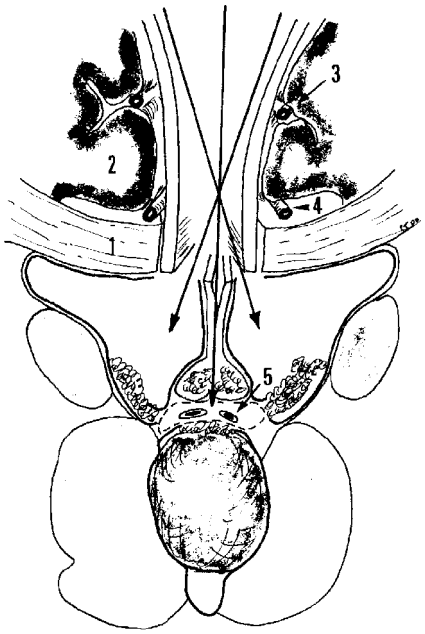


Fig. 28. Anterior transcallosal approach. (1: corpus callosum – 2: cingulate gyrus – 3: callosomarginal artery 4: pericallosal artery – 5: internal cerebral vein)

to disappear within the first month. Diencephalic lesions occur in one third of patients, with short-term memory disturbance, apraxia and anomia [28, 42].

3. Tumors of the temporal horn

[6, 8–10, 17, 25, 26, 28, 29, 34–37, 39] (Figs. 29, 30)

- Position and size of craniotomy

  The patient is placed in the supine position, either in the dorsal decubitus postion with bolsters under the ipsilateral shoulder if the spine is flexible, or in the lateral decubitus. A frontotemporal crossbow scalp, which is pulled down to the base of the temporal lobe facilitates an anterior and middle temporal craniotomy reaching the temporal floor and the pterion ventrally. The superficial sylvian vein and the vein of Labbé must be preserved.

- Access to the LV

  Several approaches to reach the LV are possible:

  – Opening of the Sylvian fissure allows access via the anterior and deep parts of its opercula towards the ventricular cavity.
  – The transsulcal T1T2 route uses a very deep sulcus which almost leads to the external wall of the LV where this is dilated. This approach is difficult and

close to the sulci vessels that must be preserved. There is major functional risk in the dominant hemisphere. It must be reserved for small tumors.
– The transcortical route uses a cortical incision through T2 rather than T1 to avoid the Sylvian fissure and to spare the T1 cortex of the dominant hemisphere

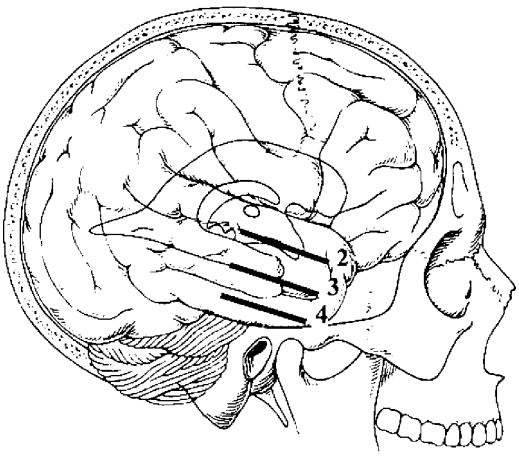


Fig. 29. Approaches to the temporal horn of the LV. (2: transsulcal T1T2 route – 3: transcortical T2 route – 4: transcortical T3 route)

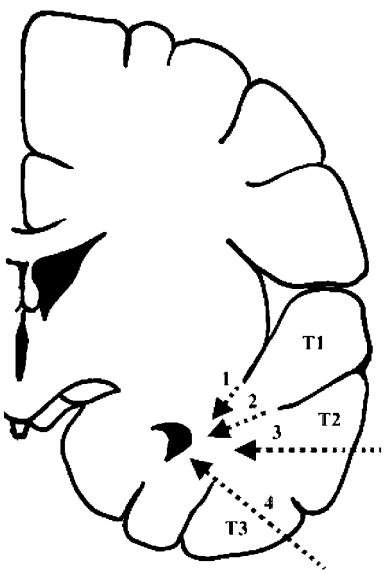


Fig. 30. Approaches of the temporal horn on a frontal section. (1: through the sylvian fissure – 2: T1T2 transulcal route – 3: T2 transcortical route – 4: T3 transcortical route)

– A cortical incision through T3 can be used with maximal rotation of the head to reach the ventricular cavity, but the vein of Labbé must be protected to avoid venous infarction. T3 is far from the language area of the dominant temporal lobe and this route avoids the anterior bundle of the optic radiations along the inferior horn. However, this route threatens the petrosal nerves. A transient partial upper-quadrant inopia can occur but it is often not perceived by patients in daily activities [39].

Each approach usually gives access to the choroidal arterial pedicle whose occlusion facilitates debulking of the tumor.

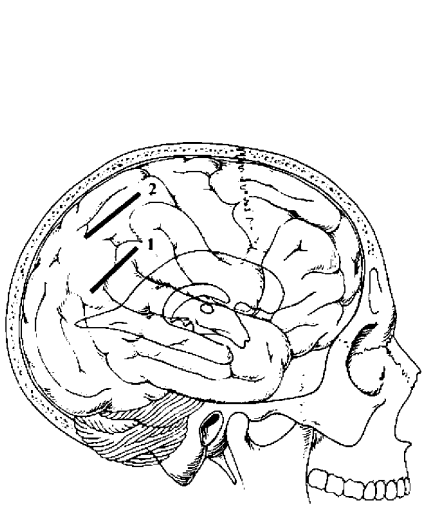
4. Tumors of the ventricular atrium

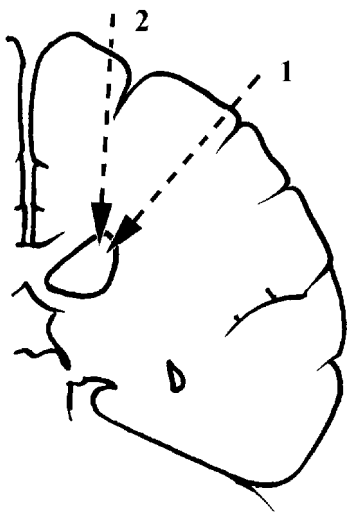
[8, 14, 17, 21, 27, 34–38, 44] (Figs. 31, 32, 33, 36, 37)

This route is easier in the minor hemisphere than in the dominant hemisphere but the campimetric risk is the same on both sides.

4.1 Minor hemisphere: transparietal route

The patient is placed in the lateral decubitus position. A parietal craniotomy centred on the atrium allows an incision through P2 towards the ventricular cavity. A high located incision is preferable to avoid the optic radiation





Figs. 31 and 32. Approaches to the atrium. (1: transparietal route – 2: posterior transparietal route) (Fig. 31, left and Fig. 32, right)

which lies ventrally opposite to the atrium (Fig. 24). Care must be taken to respect the cortical vessels and hemispheric collapse can induce the rupture of parietal or rolandic mooring veins. Retraction of the pulvinar during the procedure can lead to langage disturbances (associative cortex) [34, 35].

4.2 Dominant hemisphere: posterior transparietal approach

The projection of the language cortex requires a more dorsal and more posterior cortical incision through P1. Care must be taken not to pass the ascending parietal gyrus ventrally, and not to reach the calcarine fissure dorsally. This incision must be placed at a sufficient distance from the internal face of the hemisphere to avoid the sulci.

The patient is placed in the prone position. It is a deep approach, which necessitates the systematic use of neuronavigation to optimize the cortical incision and the orientation of the trajectory. The tumoral vascular pedicle is reached at the end of the procedure as it is located on the opposite side to the operator. After surgery, a Gertsmann's syndrome is present in 33% of patients [37].

4.3 Interhemispheric parasplenial approaches

The posterior transcallosal approach is not logical because the corpus callosum does not form the roof of the ventricular cavity dorsally. It increases the risks of posterior callosal disconnection.

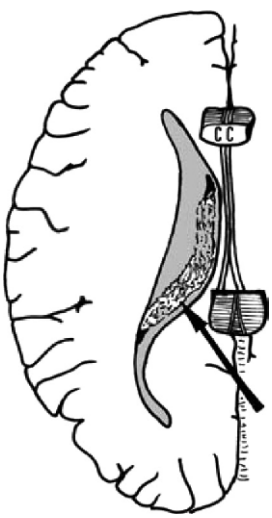
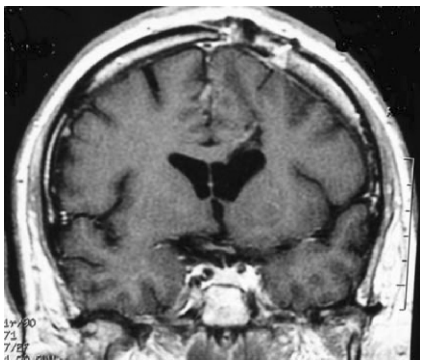
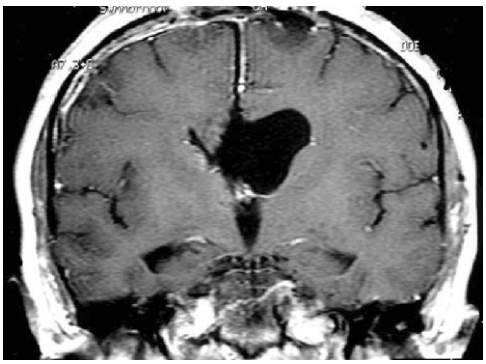


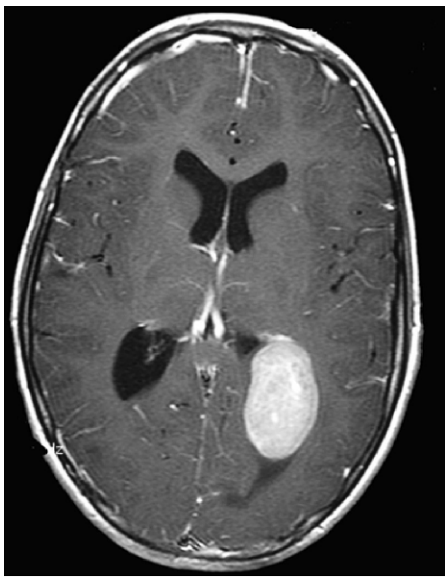
Fig. 33. Access to the atrium through the paraplenial route. (CC: corpus callosum, severed)

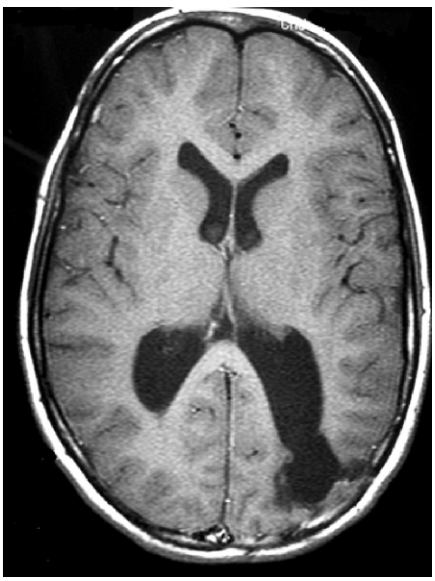
Some authors have described an interhemispheric parasplenial occipital approach, which gives access to the medial face of the atrium through the internal parietal cortex [8]. This route is performed in the prone position (Fig. 33). However it causes interruption of several bridging parietal veins and can cause hemianopia by retraction of the internal surface of





Figs. 34 and 35. Post operative MRI coronal planes after transfrontal transventricular approach (Fig. 34, left) and anterior transcallosal approach (Fig. 35, right)





Figs. 36 and 37. Atrial meningioma, preoperative MRI axial plane (Fig. 36, left), and postoperative MRI axial plane after posterior transparietal approach (Fig. 37, right)

the hemisphere. It requires an approach close to the vein of Galien, but on the other hand, allows access to the choroidal vessels at the beginning of the procedure.

5. Variants of atrium tumors

5.1 Tumors of the atrium extending to the frontal horn

Reaching the frontal horn first will expose the difficulty of approaching the atrium because of the orientation. The posterior transparietal route allows orientation of the surgical trajectory to expose the atrium and then the frontal horn. During the intervention, the removal of the tumoral portion in the atrium and the control of the vascular pedicle often allows the tumoral portion within the frontal horn to be gently teased away.

5.2 Tumors of the atrium extending to the temporal horn

For the minor hemisphere, the T1T2 transsulcal or the T2 transcortical routes can be used by extending the incision dorsally.

This cortical extension can not be used in the dominant hemisphere. The only viable route is the posterior transparietal approach with an orientation adjusted to gain access to the temporal horn. Care must be taken to control the anterior vascular choroidal pedicle.

5.3 Tumors of the atrium extending to the occipital horn

The approach of these tumors is similar to the access to the atrium except where there is a preoperative hemianopia: in this case, a transcortical occipital route in the prone position can be used.

Conclusion

The approaches to the LV are narrow and deep and often offer a limited access to the ventricular cavity especially if it is not too dilated. The preoperative planning based on the imaging must identify the main surgical difficulties and choose the best compromise between the security of the surgical procedure and the functional risks. Neuronavigation gives invaluable help when crossing the cortical mantle and remains reliable up to the opening of the ventricular cavity. The frontal horn is relatively easily accessible. On the other hand, access to the temporal horn and to the atrium may induce visual field defects and language dysfunction in operations on the dominant hemisphere.

Annexe

Table 1. *Most frequent intraventricular tumors with usual location and imaging characteristics*

Histological types	Main location	Imaging (T1-weighted MRI with gadolinium)	Main population
Meningioma	Atrium	Hyperintense lesion Homogenous	>40 years
Ependymoma	Body	Heterogenous signal Cystic component	<40 years
Central Neurocytoma	Anterior horn and body	Heterogenous signal Central calcifications	<40 years
Subependymoma	Intraventricular foramen	Hypointense signal No calcification	<40 years
Papilloma	Atrium	Asymetric hydrocephalus	Childhood
Oligodendroglioma	Anterior horn	Peripheral nodular calcifications	<40 years

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