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Part I
Advances

Neuromodulation in Cluster Headache

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Abstract Medically refractory chronic cluster headache (CH) is a severely disabling headache condition for which several surgical procedures have been proposed as a prophylactic treatment. None of them have been evaluated in controlled conditions, only open studies and case series being available. Destructive procedures (radiofrequency lesioning, radiosurgery, section) and microvascular decompression of the trigeminal nerve or the sphenopalatine ganglion (SPG) have induced short-term improvement which did not maintain on long term in most of the patients. They carried a high risk of complications, including severe sensory loss and neuropathic pain, and consequently should not be proposed in first intention.

Deep brain stimulation (DBS), targeting the presumed CH generator in the retrohypothalamic region or fibers connecting it, decreased the attack frequency >50 in 60 % of the 52 patients reported. Complications were infrequent: gaze disturbances, autonomic disturbances, and intracranial hemorrhage (2).

Occipital nerve stimulation (ONS) was efficient (decrease of attack frequency >50 %) in about 70 % of the 60 patients reported, with a low risk of complications (essentially hardware related). Considering their respective risks, ONS should be proposed first and DBS only in case of ONS failure.

New on-demand chronically implanted SPG stimulation seemed to be efficient to abort CH attacks in a pilot controlled trial, but its long-term safety needs to be further studied.

Keywords Cluster headache • Neuromodulation • Deep brain stimulation • Occipital nerve stimulation • Sphenopalatine ganglion • Trigeminal nerve

Cluster Headache

Cluster headache (CH) is a primary headache and belongs to the group of the trigeminal autonomic cephalalgias in the International Classification of the Headache Disorders (ICHD-II) [17]. CH mainly affects men and smokers and is characterized by strictly unilateral severe pain attacks associated with ipsilateral prominent parasympathetic features (conjunctival injection, lacrimation, rhinorrhea or nasal congestion, and agitation). The attacks last 15–180 min and usually occur once or several times per day. Episodic cluster headache affects 80–90 % of patients who describe periods of attacks (cluster) and periods of remission. Chronic CH (CCH) (unremitting from onset or evolved from episodic form) lacks the remissions and is diagnosed after 1 year without remission or with remission periods lasting less than

1 month [17]. Once the chronic cluster syndrome is established, the prophylactic medical treatment (verapamil, lithium) often fails to prevent the attack occurrence. The pain attack can be usually stopped by the abortive treatments (subcutaneous injection of sumatriptan, oxygen inhalation), but their use is limited. Refractory CCH is one of the most debilitating headache syndromes and is often referred to as "suicidal headache," justifying a surgical treatment.

The clinical criteria for invasive surgery (initially DBS) in CCH have been proposed by a group of experts [27]: CCH according to ICHD-II [17] for at least 2 years, at least one attack per day, resistance to pharmacotherapy (including at least verapamil and lithium), headache "locked" to the same side (this criterion does not concern occipital nerve stimulation), normal neurological examination, and absence of psychiatric comorbidity.

The pathophysiology of CH is not completely identified yet. Current hypothesis involves a trigeminal and autonomic (via the sphenopalatine ganglion) activation, explaining the trigeminal topography of pain and the ipsilateral autonomic features [15]. This activation is probably induced by a generator of attacks, potentially located in the posterior hypothalamic gray matter. Indeed, several arguments have pointed out the potential role of the hypothalamus as the central generator of the disease: (1) CH attacks occur usually with a circadian and annual rhythm [15]; (2) neuroendocrine changes are frequent in CH patients, including melatonin secretion changes; and (3) positron-emission tomography (PET) imaging during CH attacks showed a specific activation of an area located at the diencephalo-mesencephalic region, under the floor of the third ventricle [32]. Based on its projection on the Talairach grid, this region has been called posteroinferior hypothalamus. Moreover, a study in voxel-based morphometry showed an increase in gray matter density in this area [31].

Based either on empiricism or neuroscientific knowledge, surgical procedures aiming to alleviate CH symptoms, via lesion or electrical modulation, have targeted regions involved in the CH pathophysiology: trigeminal nerve or ganglion, sphenopalatine ganglion, brain stem trigemino-cervical complex, and hypothalamic nuclei or pathways.

Lesion Procedures

For patients with severe CCH refractory to medical prophylactic treatment, due to pain severity, absence of remission, and treatment resistance, surgery has been considered as a feasible option for pain control. Several lesion procedures have been tried in the past, without satisfactory long-term relief of pain.

Surgical rhizotomy [49] or section [20] of the trigeminal nerve provided immediate but not sustained improvement of pain with major sensory (severe hypoesthesia, anesthesia dolorosa, keratitis) and motor (mastication difficulties) complications. Microvascular decompression (MVD) of the trigeminal nerve eventually associated with MVD or section of the intermedius nerve (carrying parasympathetic fibers to

the sphenopalatine ganglion) has been performed in a series of 28 CCH patients [28]. Initially 73 % of them reported an improvement >50 %, but this favorable outcome did not maintain over time, despite repeated procedures. The favorable outcome might be related to nervus intermedius MVD or section, as MVD limited to the trigeminal nerve was a failure in 2/3 of the cases. Stereotactic radiosurgery (SRS) of the intracisternal portion of the trigeminal nerve has been investigated in 3 series accounting for 24 patients (mean follow-up 3 years) [9, 21, 34]. Only 5 (20 %) patients reported an improvement >50 %, but 50 % of them had facial hypoesthesia and up to 20 % developed neuropathic pain across series [9, 21]. Considering their poor results, high risk of complications and the availability of neuromodulation techniques, the lesional procedures on the trigeminal nerve should be avoided in first intention.

Associating SRS of the sphenopalatine ganglion (SPG) to trigeminal nerve SRS seems slightly more efficient than trigeminal nerve SRS alone [21]. SRS targeting only the SPG has been reported to be efficient in single cases [7, 23] and might be a promising SRS target inducing less sensory disturbances.

In two series cumulating 25 patients [37, 42], thermolesion of the SPG, using a percutaneous infra-zygomatic approach, decreased the mean frequency of CCH attacks by half (mean follow-up 12 and 24 months, respectively). However the rate of complications was high: epistaxis (80 %), lesion of the maxillary division of the trigeminal nerve (40 %), and transient hypoesthesia of the palatine area (90 %). Globally, destructive procedures on the SPG appeared more efficient on CCH attacks than lesion concerning the trigeminal nerve. These overall results encouraged the development of new nonlesional procedures targeting the sphenopalatine ganglion (see further).

Deep Brain Stimulation

Deep brain stimulation (DBS) of the posteroinferior hypothalamus has been proposed by the team of Milan [14, 25] soon after the identification of the "posteroinferior hypothalamic" activation concomitant to CH attack, with the aim to inhibit the presumed generator of pain attacks.

Results

Up to now, about 50 patients treated with DBS of this region have been reported in the literature (Table 1) [2, 11, 12, 14, 24–26, 40, 46, 47]. The overall responder rate (attack frequency decrease ≥50 %) was 60 %, including 30 % of patients being almost pain-free at longest follow-up. Only one study tried to evaluate this approach in controlled conditions [12] but failed to demonstrate a significant decrease of CH attacks between the stimulation "on" and "off" 1-month periods,

Table 1 Main studies of deep brain stimulation for refractory chronic cluster headache

Author	Patients (*n*)	Follow-up (years)	Almost pain-free patients (*n*)	At least ↓ attack frequency >50 % (*n*)	Complications
Leone [14, 24–26]	17	8.7	6	6	Electrode misplacement (2) or malpositioning (1), infection (4), ICH (1), seizure (1), permanent weakness (1)
Schoenen [43]	6	4	2	1	Fatal ICH (1); panic attack (1); oculomotor disturbances
Starr [47]	4	1	0	2	Oculomotor disturbances, transient loss of consciousness
Owen [40]	1	0.7	1	0	–
Bartsch [2]	6	1.4	2	1	–
Fontaine [11, 12]	11	1	3	3	Oculomotor disturbances (3), transient loss of consciousness (1), micturition syncopes (1)
Seijo [46]	5	2.8	2	3	Euphoria, oculomotor disturbances, headache, increased appetite, cervical dystonia
Total	52		16 (30 %)	16 (30 %)	

due to the too short duration of these periods. Indeed, the therapeutic effect of retro-hypothalamic DBS may be delayed, the mean time to obtain a clinically significant headache reduction ranging from 1 to 86 days. Several authors have reported that few patients with long follow-up displayed few bouts of attacks per year, similar to an episodic CH.

Technical Aspects, Anatomical Concerns, and Mechanisms of Actions

Surgery may be conducted under general or under local anesthesia which allows a preoperative stimulation to assess eventual side effects, especially gaze disturbances. The use of microelectrode recordings (MER) is not recommended because it does not bring additional information useful to optimize electrode placement and increases the risk of intracerebral hemorrhage (ICH). Common stimulation parameters used for chronic stimulation are frequency 130 Hz, pulse width 60–210, and amplitude 1.5–3.5 V.

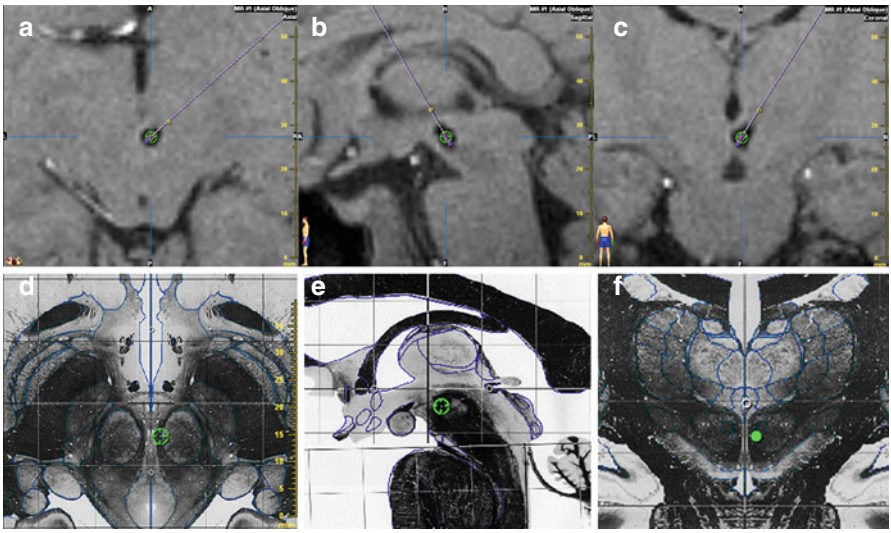

Fig. 1 Postoperative T1-weighted MRI in chronic refractory cluster headache patient treated by deep brain stimulation of the retro-hypothalamic region. Intended stereotactic target (*green circle*) ($x=2$ mm; $y=-3$ mm; $z=-5$ mm, relative to the mid-commissural point) is projected within the artifact generated by the electrode on axial (**a**), sagittal (**b**), and coronal (**c**) slices and on the corresponding sections of the Schaltenbrand atlas (**d**–**f**)

The functional target of DBS in CCH is virtual and is consequently defined indirectly using its stereotactic coordinates according to the bi-commissural plan. The most often used target has been initially proposed by Franzini et al. [14] and is located 2 mm lateral to the midline, 3 mm posterior to the mid-commissural point (MCP), and 5 mm below MCP (Fig. 1). A useful anatomic landmark visible on MRI is the anteromedial border of the red nucleus. The neural structure corresponding to these coordinates and whose stimulation induces the therapeutic effect is still debated. An anatomical study of electrode locations has identified several candidate structures [11], including the mesencephalic gray substance and several fascicles connecting the hypothalamus with the autonomic nuclei of the brain stem (Fig. 2). Moreover, the electrode location did not differ between responders and nonresponders, suggesting that other factors not related to electrode misplacement may be responsible for failure of DBS treatment in nonresponders.

However, two additional neighboring targets seem to be efficient. The first one is actually located in the posterior hypothalamus (4 mm from the third ventricle wall, 2 mm posterior to and 5 mm below the MCP) [46]. Ventriculography-guided implantation of electrode on the floor of the third ventricle via the foramen of Monro was also efficient [3].

Tractography studies confirmed that DBS targets for CCH were located close to fibers connecting the hypothalamus with the brain stem [39, 40]. A positron emission

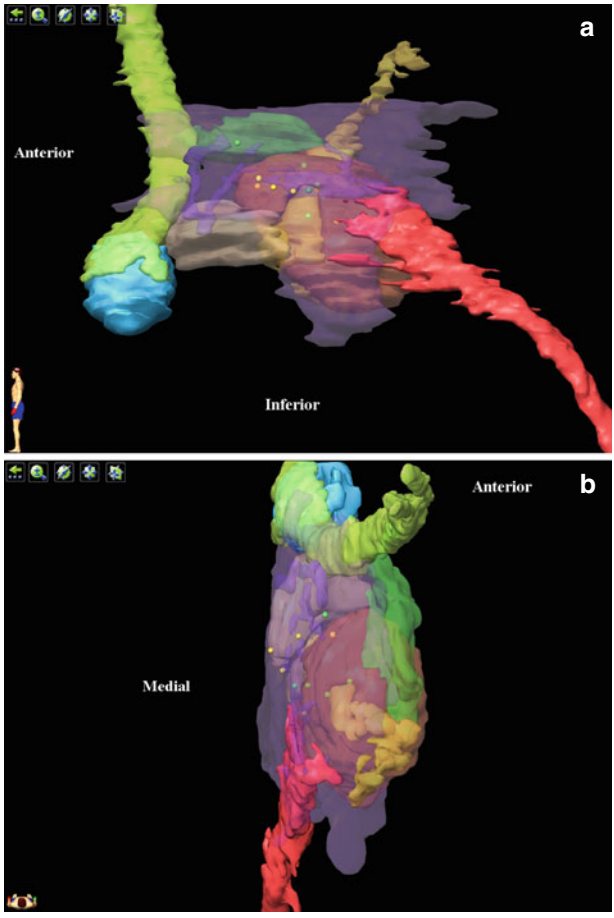

Fig. 2 Location of DBS electrodes on 3D rendering of relevant anatomic structures of the retrohypothalamic region, from medial (**a**) and superior (**b**) views, in a series of 11 refractory cluster headache patients [11]. Contacts of responders are in green and nonresponders in yellow. The region of interest is centered by the red nucleus (transparent, *orange*). Medially, the mesencephalic gray substance (transparent, *purple*) belongs to the wall of the third ventricle and is in continuity with the posterior hypothalamus anteriorly and with the periaqueductal gray substance posteriorly. The mammillary body (*light blue*), with the mammillothalamic fascicle (*light green*) and the mammillotegmental fascicle (transparent, *dark green*), constitutes the macroscopic posterior border of the hypothalamus. The ventral tegmental area (*beige*) is located immediately posterior to the mammillary bodies. Several bundles cross this area. The fascicle retroflexus of Meynert (*yellow*, transparent) makes a notch in the medial region of the red nucleus and links the habenula with the interpeduncular nucleus. The medial longitudinal fascicle (*red*) connects the hypothalamus with autonomic centers in both the brain stem and spinal cord. The dorsal longitudinal fascicle (transparent, *purple*; only thin portions are individualized at this level) connects the paraventricular nucleus of the hypothalamus with the periaqueductal gray matter, the locus coeruleus, and autonomic centers of the brain stem. Several structures have been erased for simplification

study comparing retro-hypothalamic DBS "on" and "off" conditions showed that the stimulation induced activation in the ipsilateral posterior hypothalamic gray (site of electrode implantation), ipsilateral thalamus, somatosensory cortex and precuneus, anterior cingulate cortex, and ipsilateral trigeminal nucleus and ganglion [33].

Plotted together, these data suggest several putative mechanisms of action for DBS in CCH: (1) inhibition of a CH generator actually located in the hypothalamus and modulated through stimulation of afferent fibers in the retro-hypothalamic area; (2) inhibition of a CH generator located in the retro-hypothalamic region or in the mesencephalic gray substance; and (3) modulation of nonspecific antinociceptive systems, including mesencephalic gray substance or orexinergic system [18].

Complications

Few stimulation-related side effects have been reported: sensation of imminent death, transient loss of consciousness with palsy (stimulation of reticular formation?), micturition syncope, and gaze disturbances (probably related to the stimulation of supranuclear gaze control pathways including rostral interstitial nucleus of medial longitudinal fascicle and interstitial nucleus of Cajal). Two ICH (one death and one permanent neurological deficit) have been reported in early series using MER, probably related to the injury of the paramedian thalamo-peduncular deep penetrating midbrain vessels.

However, considering the high risk of ICH in pioneer DBS studies, some centers rapidly abandoned DBS and opted to a less invasive procedure as occipital nerve stimulation (ONS).

Occipital Nerve Stimulation

The principle of ONS is to deliver a continuous electrical stimulation to the greater occipital nerve (GON) (Fig. 3) and/or to the lesser occipital nerve (LON), via a subcutaneous chronically implanted electrode adjacent to the nerve and connected to a generator. ONS induces paresthesias in the occipital region. Originally described by Weiner [53] to control occipital nerve neuralgia, this technique has been proposed to treat primary headaches, including CCH.

Results

ONS for CCH has been studied only in open trials (Table 2) [4–6, 13, 29, 30, 36, 48]. The overall success rate (attack frequency decrease >50 %) was about 75 %, and most of the patients would recommend the operation to a fellow CCH patient. ONS

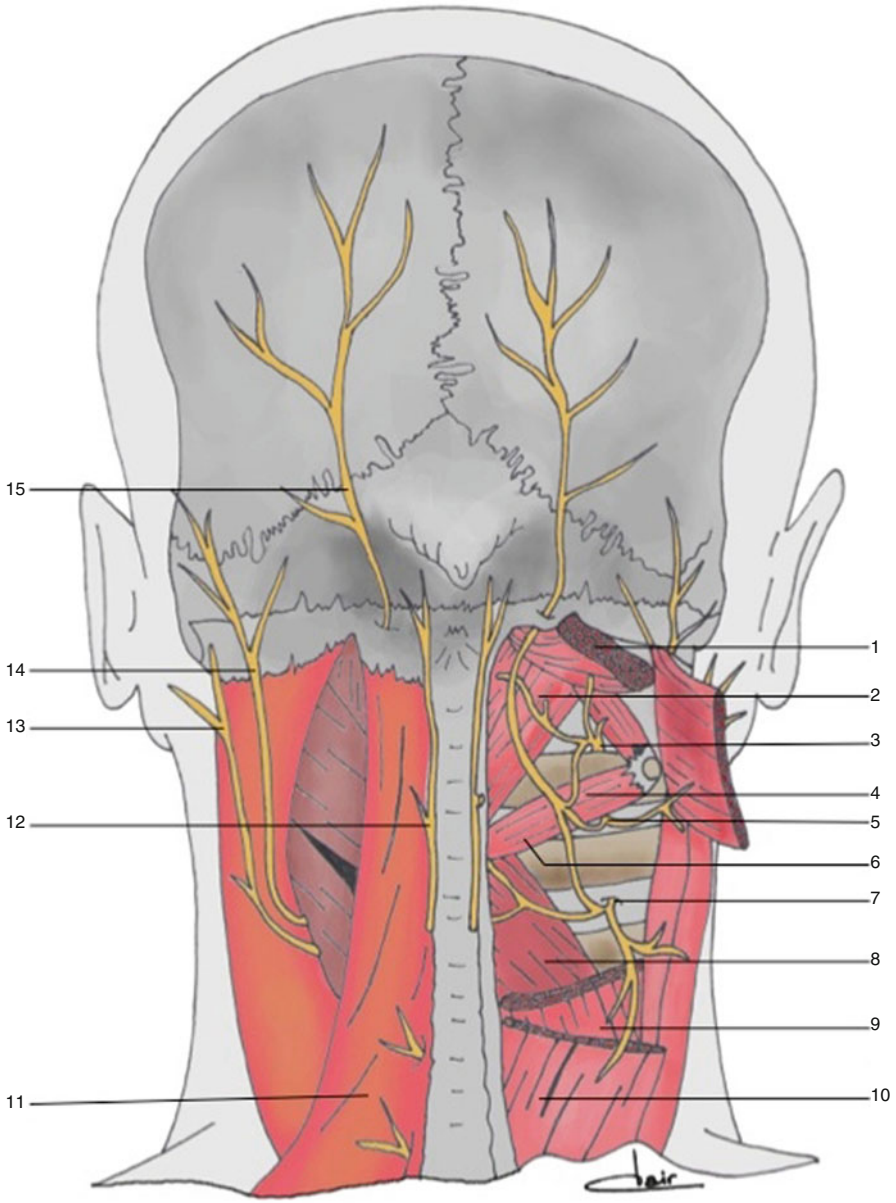

Fig. 3 Anatomy of the occipital and suboccipital regions. *1* Head semispinalis muscle (cut and retracted), *2* rectus posterior muscle of the head, *3* dorsal ramus of C1, *4* head inferior oblique muscle, *5* dorsal ramus of C2, *6* inferior oblique muscle, *7* dorsal ramus of C3, *8* partial section of the head muscle, *9* partial section of the neck muscle, *10* splenius muscle of the head, *11* trapezius muscle, *12* third occipital nerve, *13* great auricular nerve, *14* lesser occipital nerve, *15* greater occipital nerve

Table 2 Main studies of occipital nerve stimulation for chronic cluster headache

Study	Patients (*n*)	Mean follow-up [range] (months)	Recommend the operation	Improved >50 % (*n*)	CH attack frequency	CH attack intensity	Treatment decreased
Burns et al., 2007 [4] and 2009 [5]	14	17.5 [4–35]	11/14	10/14	−33 %	+8 %	6/14
Magis et al., 2007 [29] and 2011 [30]	15	36.8 [11–64]	10/15	12/15	−94.6 %	–	4/14
De Quintana et al., 2010 [6]	4	6 [ ]	4/4	4/4	−56 %	−48.8 %	3/4
Müller, 2011	10	12 [3–18]	–	6/10	−40.3 %	−28.6 %	3/10
Fontaine et al., 2011 [13]	13	14.6 [3–34]	12/13	10/13	−68.2 %	−48.9 %	8/13
Strand et al., 2011 [48]	3	10 [6–12]	–	2/3	−61 %	–	
Total	59		37/59 (63 %)	44/59 (75 %)			24/45 (53 %)

acts like a prophylactic treatment, decreasing the frequency of the CH attacks and their intensity and allowing to decrease the prophylactic drugs in most of the patients, but does not stop the attack once it has begun. Considering their respective risks of complications, ONS should be proposed before DBS in refractory CCH patients.

The feeling of paresthesias appears mandatory to obtain a clinical improvement. Consequently a placebo effect cannot be ruled out, even if its probability is low. However, it will be difficult to show the ONS efficacy in controlled and blinded conditions because the patients perceive ONS-induced paresthesias. Patients who do not feel the paresthesias anymore (lead migration, dysfunction, etc.) often describe a recurrence of their headache attacks within the following days.

ONS has been proposed to treat other medically refractory primary headache, including chronic migraine.

Technical Aspects

The original technique described the implantation of a transverse cylindrical thin electrode crossing the midline from a retro-mastoid incision, allowing to stimulate both sides with one electrode. Multiple variations of this technique have been reported in the literature (Fig. 4), using one or two electrodes, percutaneous cylindrical electrodes or surgical paddle ones, approach from the midline or from one or two retro-mastoid incision(s) [10, 22, 39, 41, 50–53]. Results and complications seemed to be similar whatever the technique was, and no comparative study is available claiming the superiority of one technique over others.

However, in our opinion, several major technical considerations have to be respected. First the subcutaneous electrodes have to cross the nerve in its superficial course. Although there is a great interindividual anatomical variability, the GON becomes superficial after piercing the fascia of the semispinalis capitis muscle (27 mm below the occiput, 12 mm from the midline in average) or the trapezius muscle (9 mm below the occiput, 35.5 mm from the midline in average) and follows then a laterally and superiorly oriented course [38] (Fig. 3). Consequently the “right spot” to place the stimulating electrode contacts would be located approximately 0–1 cm below the occiput and 2–4 cm from the midline. There is no data demonstrating that ONS efficacy in CCH is correlated specifically to the stimulation of GON, LON, or both or correlated to the surface of ONS-induced paresthesias. Consequently, ONS electrodes may be implanted as well under local or general anesthesia, per or intra-operative stimulation not being mandatory in our experience to optimize the electrode placement.

The electrodes have to be implanted subcutaneously above the fascia. Implanting the electrode too superficially or too deep would increase the risk of skin erosion/electrode exteriorization or muscle spasms/unpleasant contractions, respectively. As electrode migration is the most frequent complication, the leads have to be anchored firmly to the epifascial plane, using non-resorbable sutures. Performing one or two loops with the leads is recommended to allow extension of the leads

during cervical movements. Although the internal pulse generator may be implanted in the buttock and the lower abdomen of the infraclavicular pectoral regions, the risk of migration might be higher with the buttock site due to excessive lead elongation during movements [50].

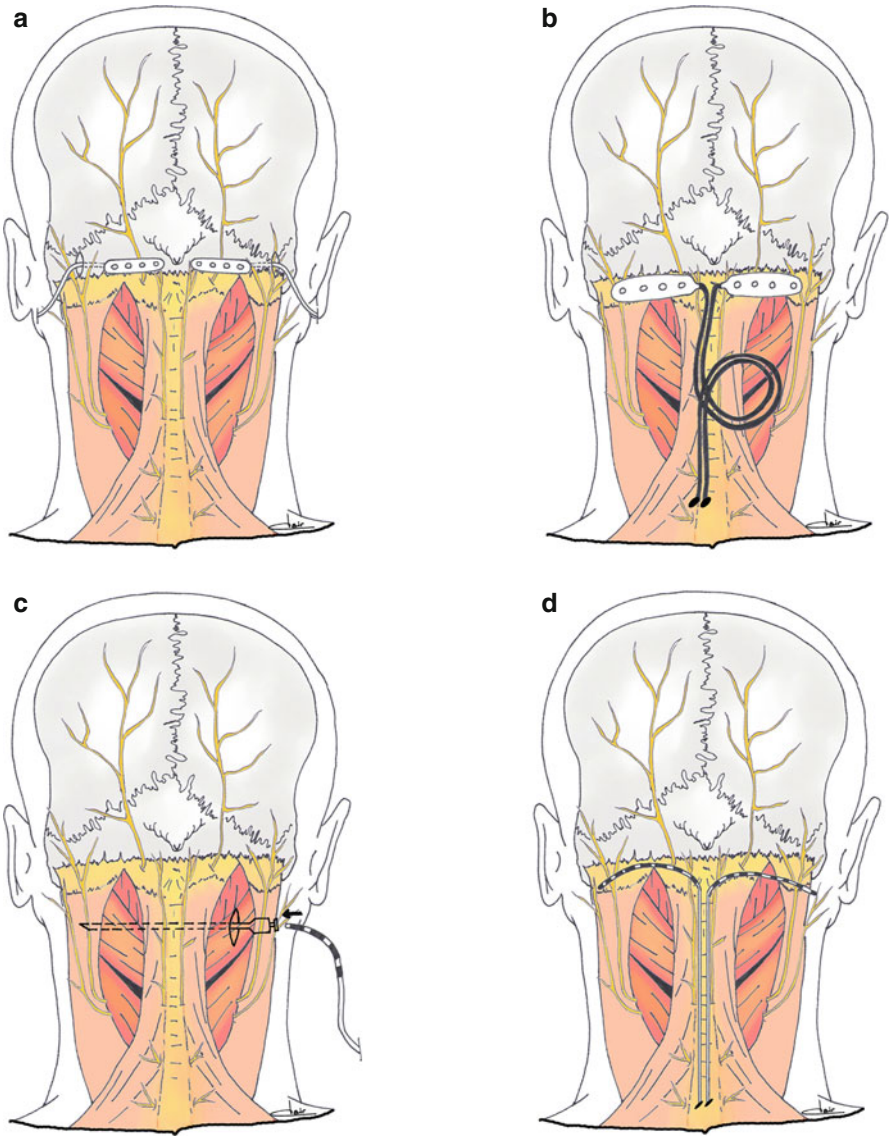

Fig. 4 Examples of different techniques proposed in the literature for bilateral implantation of great occipital nerve stimulation electrodes. Paddle electrodes (**a**, **b**) may be implanted using lateral [39] or midline [22] approaches. Cylindrical (**c**–**e**) electrodes may be implanted percutaneously from lateral [52, 53] or midline [10] entry points

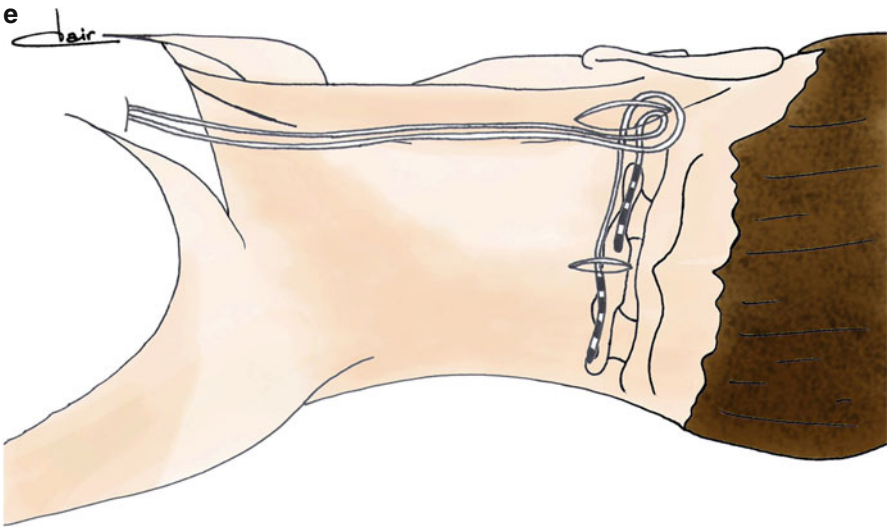

Fig. 4 (continued)

Bilateral stimulation is recommended to treat primary headache to avoid headache side-shift, which has been reported in up to one-third of the patients stimulated unilaterally [29, 30]. Trial stimulation is not useful because some patients can improve after several months of continuous stimulation [13]. Response to occipital nerve block is not useful in predicting the ONS efficacy [45].

Complications

ONS carries a low risk of minor surgical complications. Early studies reported a high rate (25–100 %) of electrode migration due to neck movements, justifying a strict technique to anchor the leads. The risk of superficial infection is about 3 %. Most of the patients develop tolerance, meaning that they have to progressively increase the stimulation intensity to continue to feel the paresthesias. This phenomenon leads to high current consumption and consequently to a rapid battery depletion, leading to frequent battery changes or implantation of rechargeable generator, increasing the cost of the technique.

Mechanisms of Action

The exact mechanisms of action of ONS in CH are still unknown. Several arguments suggest that ONS could act through modulation of convergent nociceptive inputs in the trigemino-cervical complex, involving a “gate control theory-like” mechanism [16].

About one-third of the CCH patients successfully treated by ONS have still autonomic attacks without pain [30]. This suggests that ONS might act through a nonspecific modulation of central pain control systems rather than through modulation of a central CH generator. A functional imaging study performed in ONS responders has shown metabolic changes in the "pain matrix" regions but the persistence of an ipsilateral hypothalamic activation, confirming that ONS does not act on the CH hypothalamic generator [30].

Stimulation of the Sphenopalatine Ganglion (SPG)

Sphenopalatine Ganglion Anatomy

The cranial autonomic symptoms associated with CH attacks probably result from the activation of a trigeminal autonomic reflex [15]. The parasympathetic efferent component of this reflex is mediated, at least in part, through the SPG. The SPG is located in the pterygopalatine fossa (PPF), behind the posterior wall of the maxillary sinus, and is bordered posteriorly by the pterygoid process, superiorly by the sphenoid sinus, and medially by the palatine bone (Fig. 5). Laterally it communicates with the infratemporal fossa. The foramen rotundum, from which the maxillary division of the trigeminal nerve exits, is located superolaterally within the PPF. The SPG contains sensory, parasympathetic, and sympathetic fibers.

SPG Procedures in CH

Several lesioning procedures involving the SPG have been proposed for the treatment of CCH. The success rates of ganglionectomy and radiofrequency lesioning or blocks varied from 46 to 85 % [8, 35, 37, 42]. However, repeated access to the SPG has been required because, in most of the cases, the benefits are transient. Indeed, in destructive procedures, pain often recurs, perhaps because alternative nerve connections are reconstituted over time. Additionally, long-term sequelae such as sensory loss and dysesthesias have been reported.

Stimulation of the SPG in CCH

A first case of chronic SPG stimulation for the treatment of CH with an implantable device was published in 2007 [19]. The report noted marked reduction in pain with acceptable safety. The only complication reported was hardware failure, during which the patient's headaches worsened. After hardware replacement, the

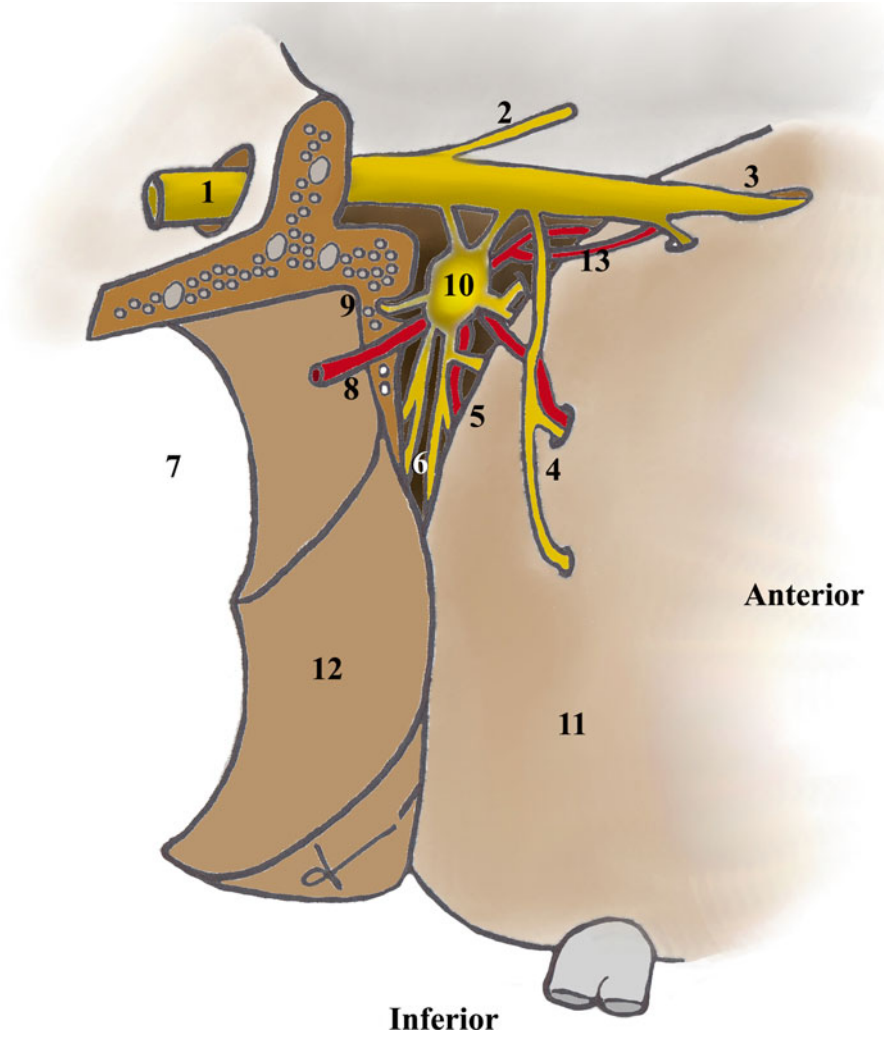

Fig. 5 Anatomical schematic drawing of the right sphenopalatine ganglion within the pterygomaxillary fossa. *1* Maxillary nerve, *2* zygomatic nerve, *3* infraorbital nerve entering its canal, *4* alveolar nerves and artery, *5* descending palatine artery in the pterygomaxillary fossa, *6* palatine nerves, *7* infratemporal fossa, *8* internal maxillary artery, *9* vidian nerve in its canal, *10* sphenopalatine (or pterygopalatine) ganglion in its fossa, *11* maxillary tuberosity, *12* lateral pterygoid plate, *13* sphenopalatine and infraorbital arteries

patient experienced again an improvement in the headaches, strongly suggesting the efficacy of the SPG stimulation. More recently, Ansarinia published a proof of concept study on the response of CH patients to acute SPG stimulation [1]. Effective abolition of induced CH attack was reported within 3 min of SPG stimulation.

With these SPG stimulation experiences in mind, a chronically implantable neuromodulation device, specifically designed for acute SPG stimulation, has been developed, in order to abort the CH attacks on demand. The neurostimulator device is implanted in the PPF, along the posterior wall of the maxillary bone, fixed to the zygomatic process with a screwed plate, the lead being placed in contact with the SPG. The neurostimulator does not contain battery but is activated and powered by a remote controller using radiofrequency energy.

The efficacy and safety of this on-demand abortive SPG stimulation device have been very recently assessed in a multicenter randomized, sham-controlled study, in 28 patients suffering from refractory CCH [44]. Each CH attack was randomly treated with full, sub-perception, or sham stimulation. Pain relief was achieved in 67.1 % of full stimulation-treated attacks compared to 7.4 % of sham-treated and 7.3 % of sub-perception-treated attacks ($p < 0.0001$). Nineteen of 28 (68 %) patients experienced a clinically significant improvement, but only 32 % achieved a pain relief in more than 50 % of the treated attacks, and 43 % experienced a reduction >50 % of attack frequency. Most patients (81 %) experienced transient, mild/moderate loss of sensation within the maxillary (V-2) nerve territory, resolving in most of the patients within 3 months. Further developments of this technique and studies comparing efficacy and safety of SPG stimulation with ONS are needed.

Conclusion

Medically refractory CCH is a severely disabling headache condition for which several surgical procedures may be proposed as prophylactic treatment. None of them have been evaluated in controlled conditions, only open studies and case series being available. Destructive procedures on the trigeminal nerve or the SPG may induce short-term improvement which does not maintain over time in most of the patients. Due to the high risk of complications, including severe sensory loss and neuropathic pain, they should not be proposed in first intention. Retro-hypothalamic DBS and ONS are efficient (decrease of attack frequency >50 %) in about 60–70 % of the patients. Considering the respective risks of ONS and DBS, ONS should be proposed first and DBS should be considered only in case of ONS failure. New on-demand implanted SPG stimulation seems to be efficient to abort CH attack, but its long-term safety needs to be further studied.

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Occipital Nerve Stimulation

Antonios Mammis, Nitin Agarwal, and Alon Y. Mogilner

Contents

Abstract Occipital nerve stimulation (ONS) is a form of neuromodulation therapy aimed at treating intractable headache and craniofacial pain. The therapy utilizes neurostimulating electrodes placed subcutaneously in the occipital region and connected to a permanently implanted programmable pulse generator identical to those used for dorsal column/spinal cord stimulation. The presumed mechanisms of action involve modulation of the trigeminocervical complex, as well as closure of the physiologic pain gate. ONS is a reversible, nondestructive therapy, which can be

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tailored to a patient's individual needs. Typically, candidates for successful ONS include those patients with migraines, Chiari malformation, or occipital neuralgia. However, recent MRSA infections, unrealistic expectations, and psychiatric comorbidities are generally contraindications. As with any invasive procedure, complications may occur including lead migration, infection, wound erosion, device failure, muscle spasms, and pain. The success of this therapy is dependent on careful patient selection, a preimplantation trial, meticulous implantation technique, programming strategies, and complication avoidance.

Keywords Occipital Nerve Stimulation • Headache • Pain • Migraine • Occipital Neuralgia

Introduction

Early interest in neurostimulation for headache and facial pain focused on deep brain targets. In 1973, Hosobuchi, Adams, and Rutkin described the use of thalamic stimulation to treat facial anesthesia dolorosa [4]. In 1976, Mazars and Pull, described intermittent stimulation of the ventroposterolateral nucleus of the thalamus (nVPL) to treat intractable headache [12]. Recent trends, however, have shifted focus from central to peripheral targets.

In 1997, Goadsby reported that stimulation of the greater occipital nerve (GON) in cats resulted in increased metabolic activity of the trigeminal nucleus caudalis and cervical dorsal horn [2]. These were among the first experiments to implicate the role of the GON in modulating the trigeminal system. In 1999, Weiner reported that stimulation of the greater occipital nerves can alleviate pain associated with occipital neuralgia [21]. In 2004, Goadsby reported that occipital nerve stimulation was efficacious in treating chronic migraine, sparking further interest in utilizing peripheral neurostimulation (PNS) in a number of headache and craniofacial pain syndromes [5, 6, 11, 13, 14, 17].

A variety of occipital headache or pain syndromes may be effectively treated with ONS (Fig. 1). The authors review the pathophysiology, patient selection, surgical technique, device programming, and potential complications associated with occipital nerve stimulation as a minimally invasive therapeutic strategy.

Pathophysiology

Neuromodulation refers to alteration of electrical or chemical activity of the peripheral or central nervous system for relief of pain through the process of inhibition, stimulation, modification, or other forms of regulation. ONS is a form of neuromodulation, which is reversible, adjustable, and may be individualized to the patient's specific therapeutic needs. While the mechanisms of action for the pain

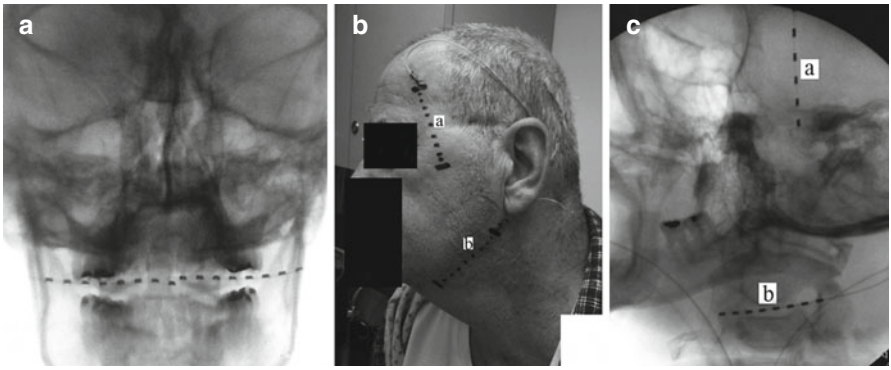

Fig. 1 Intraoperative anterior-posterior (AP) radiograph demonstrating bilateral placement of octrode neurostimulator arrays (**A**). This patient is a 58-year-old male who developed left V1 and V3 distribution pain, after a brain stem infarct. Trigeminal branch stimulation, a form of peripheral field stimulation, trial leads were placed in V1 (*a*) and V3 (*b*) regions, corresponding to the painful areas (**B**). Intraoperative lateral radiograph of the same patient demonstrating final position of the implanted V1 (*a*) and V3 (*b*) region leads (**C**)

relief obtained from an ONS are incompletely understood, the following are thought to play some role: subcutaneous electrical conduction, dermatomal stimulation, myotomal stimulation, sympathetic stimulation, local blood flow alteration, peripheral nerve stimulation, peripheral or central neurochemical mechanisms, and the trigeminovascular system or trigeminocervical tract. Ultimately, peripheral neurostimulation may exert its effect by multiple mechanisms, which may differ in the various headache and pain syndromes [7].

One theory postulates the involvement of the trigeminocervical system – the anatomic overlap of the trigeminal and occipital afferent systems at the spinal cord vertebral level of C_2. These afferents have been cited to converge on second-order nociceptors in the spinal trigeminal nucleus. As such, trigeminal afferent pathways, and thereby primary headache disorders, may be controlled at the C_2 level by occipitally mediated afferents. Others suggest that electromodulation reduces blood flow to areas of pain as well as abnormal excitation of the peripheral pain fibers. Therefore, the central sensitization of the trigeminal sensory nerve pathways is prevented, while the descending system at the level of the dorsal horn may be modulated.

Another possible mechanism of action of ONS is described by the gate control theory. Described initially by Melzack and Wall in 1965, the gate control theory describes the enhancement of inhibitory actions of the local circuit neurons in the dorsal horn on the central transmission cells. Stimulation of somatosensory pathways, such as the peripheral nerves or dorsal columns, results in activation of large myelinated afferents (Aß fibers), which "close the pain gate" in the substantia gelatinosa, by enhancing the inhibitory actions of local circuit neurons in the dorsal horn on central transmission cells. The preferential activation of larger, myelinated Aß fibers thus reduces nociceptive transmission in the smaller, thinly myelinated and unmyelinated A∂ and C fibers, effecting a reduction in pain.

Patient Selection

Occipital nerve stimulation has been used for the management of a variety of headache disorders, including Chiari I malformation headache, migraine headache, cluster headache, cervicogenic headache, occipital neuralgia, and posttraumatic headache. In a recent publication by the authors, a single center's experience with ONS was analyzed, with patients being retrospectively diagnosed (Table 1). The authors have observed that with those patients with the following conditions, a substantial success rate was expected: migraine, Chiari malformation, and occipital neuralgia. However, patients with recent MRSA infections, unrealistic expectations, and psychiatric comorbidities are those who are generally avoided. These issues underscore the importance of using a trial and requiring a psychiatric evaluation for all patients [10].

Utilizing ONS, Schwedt et al. demonstrated that 60 % of patients treated for various chronic headache syndromes experienced a 30 % reduction in headache frequency and severity [15]. Additionally, Popeney and Aló reported that 85 % of patients with transformed migraine showed over a 50 % reduction in frequency or severity of the headache following neurostimulation [13]. Multiple studies have also explored the treatment of occipital neuralgia with ONS, including one by Slavin et al. that described benefits in 70 % of the patients treated for occipital neuralgia [17]. Whiplash-related headaches, traumatic nerve injuries, or cluster headaches may also be treated with ONS after failed attempts with just medical management. In one prospective study, Schoenen et al. demonstrate potential for ONS to be an effective treatment strategy for drug-resistant chronic cluster headaches. Of the eight patients enrolled, two patients were pain free on long-term follow-up and three exhibited a substantial reduction in the frequency of attacks. Moreover, none of the patients experience any serious adverse [8]. ONS has been shown to be beneficial in headache attributed to Chiari malformation. In patients who have undergone suboccipital decompression, but continue to have headaches, ONS should also be considered. This approach has been documented as a therapeutic modality for chronic occipital and suboccipital in patients with Chiari I malformation. In retrospective analysis of 22 patients with Chiari malformation, 68 % of patients (15 of 22) successfully underwent a trial of ONS. Following these trials, 87 % (13 of 15) of those who received permanent implantation reported continued pain relief [20].

Migraine affects an estimated 12 % of US population. Of those who suffer from migraines, about 70 % are women. Approximately 3–13 % of migraine patients progress to chronic migraine [11]. These patients claim they have headache pain more than 15 days per month. Though less common than migraine, other conditions such as occipital neuralgia and cluster headache can be quite disabling, and may progress to chronic, intractable states. Of those who cope with headaches, approximately 5 % suffer from daily headaches (transformed migraine and chronic daily headaches). Moreover, 1–2 % may be poorly responsive to medical treatment modalities. Attempted continuity of medical management may lead to hopelessness,

Table 1 Patient outcomes from a study by Mammis et al. on Peripheral Neuromodulation for Headache and Craniofacial Pain [10]. For each diagnosis, codes from the 2nd edition of the International Headache Classification (ICHD-2) system are listed

ICHD-2: Diagnosis	Number of patients	Number of successful trials	Trial success rate (%)	Number of permanent systems still used at last follow-up	Long-term implanted success rate (%)	Intent-to-treat success rate (%)
7.7: Headache attributed to Chiari malformation type I	28	18	64	15	83	54
1.1 or 1.2: Migraine headache with or without aura	24	21	88	19	90	79
5.2.2: Chronic posttraumatic headache attributed to mild head injury	11	10	91	8	80	73
13.8: Occipital neuralgia	8	7	88	7	100	88
5.7.2: Postcraniotomy headache	7	7	100	6	86	86
3.1.2: Chronic cluster headache	5	4	80	4	100	80
6.1.1: Headache attributed to ischemic stroke	5	3	60	1	33	20
13.7: Other trigeminal or terminal branch neuralgias	5	4	80	1	25	20
11.2.1: Cervicogenic headache	4	3	75	3	100	75
4.7: Hemicrania continua	1	1	100	1	100	100
7.4.4: Headache attributed to hypothalamic or pituitary hyper- or hyposecretion	1	1	100	0	0	0
7.7: Headache attributed to Chiari malformation type I	28	18	64	15	83	54
1.1 or 1.2: Migraine headache with or without aura	24	21	88	19	90	79
5.2.2: Chronic posttraumatic headache attributed to mild head injury	11	10	91	8	80	73
13.8: Occipital neuralgia	8	7	88	7	100	88
5.7.2: Postcraniotomy headache	7	7	100	6	86	86
3.1.2: Chronic cluster headache	5	4	80	4	100	80
6.1.1: Headache attributed to ischemic stroke	5	3	60	1	33	20
13.7: Other trigeminal or terminal branch neuralgias	5	4	80	1	25	20
11.2.1: Cervicogenic headache	4	3	75	3	100	75
4.7: Hemicrania continua	1	1	100	1	100	100
7.4.4: Headache attributed to hypothalamic or pituitary hyper- or hyposecretion	1	1	100	0	0	0

despair, activity restrictions, and narcotic dependence. Ultimately, patients who have failed medical therapy and have headache pain refractory to preventative medication are candidates for ONS trials. A recent double-blinded randomized trial of ONS for migraine headache demonstrated significant differences between the groups in reduction of number of headache days, migraine-related disability, and direct reports of pain relief [16].

Surgical Technique

Similar to dorsal column stimulation, a trial is usually performed prior to a permanent implant. The patient may be positioned laterally or prone based on the location of the skin incision. For the trial, a percutaneous lead is introduced under fluoroscopic guidance with the patient under sedation (Fig. 2). The entry point should be approximately 1 cm superior to the tip of the mastoid process, and the trajectory is towards the tip of the odontoid process. Trajectories superior to this are often used and are well tolerated. The electrode should be placed in the superficial aspect of the subcutaneous fat. Care should be taken to not place the lead in the dermis, nor too close to the fascia. The leads are secured to the skin with a 2-0 nylon drain stitch. The leads are then inserted into the trialing cable and programming commences. Stimulation is applied using a temporary radiofrequency (RF) transmitter to various select electrode combinations; this enables the patient to report the stimulation location, intensity, and overall sensation. Most patients have reported an immediate stimulation in the selected occipital nerve distribution with 1–4 V with midrange pulse widths and frequencies. The trial period is typically 4–7 days,

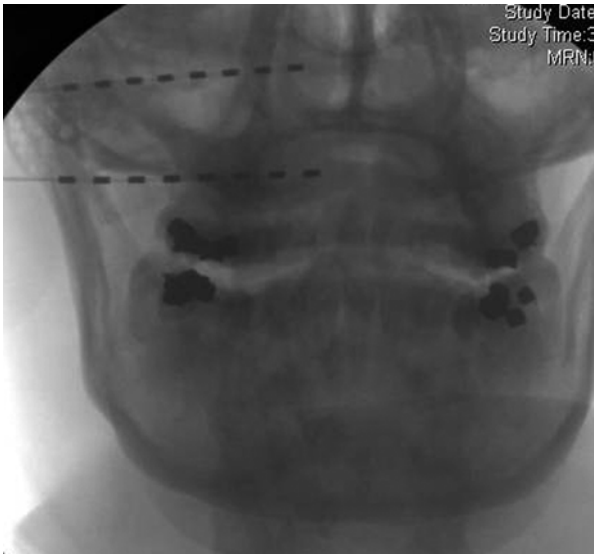

Fig. 2 Intraoperative AP radiograph demonstrating stacked occipital percutaneous trial leads in a patient with hemicrania continua

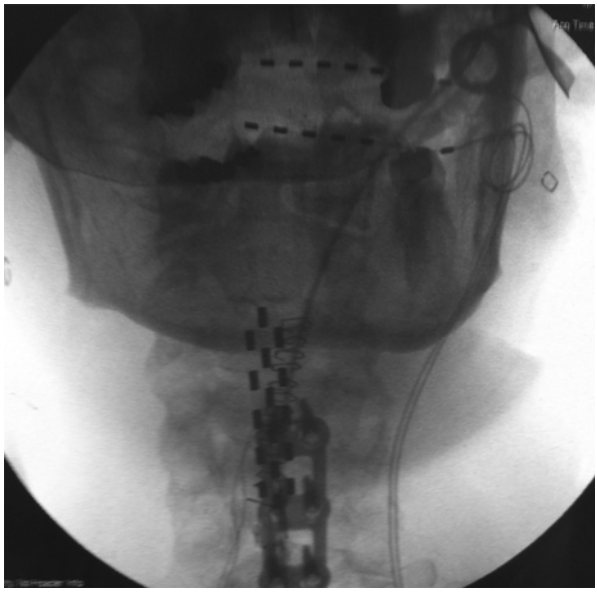

Fig. 3 AP radiograph demonstrating implanted stacked occipital leads and a cervical paddle electrode in a patient with chronic migraine and complex regional pain syndrome of the right upper extremity

and patients are encouraged to maintain a headache or pain diary. Trial success is defined as greater than 50 % improvement in pain on the visual analog scale, significant reduction in headache days, or improvement in quality of life.

Upon a successful trial of neurostimulation, permanent implantation may be considered (Fig. 3). We perform permanent implantation under general anesthesia. The patient is positioned supine with the head turned towards the left. A retroauricular incision is made on the right side and dissection is carried down to the retromastoid fascia. A small pocket is made within the subcutaneous tissue immediately lateral to the incision to accept a loop of electrode created after placement and tunneling in order to prevent electrode migration. An additional stab incision is made in the midline. A Tuohy needle is curved to conform to the transverse posterior cervical curvature (bevel concave). The needle is passed, without further dissection, transversely in the subcutaneous space across the base of the affected greater and/or lesser occipital nerves, from the midline stab incision towards to left side. A lead is introduced and the needle is withdrawn. Care should be taken to not stab through the skin. The needle is then placed from the retromastoid incision to the midline incision, and the wire is placed through the needle. Upon withdrawing the needle, the lead is tunneled to the retromastoid incision. The lead is then anchored to the retromastoid fascia with silk stitches. The needle is then introduced from the retromastoid incision to the midline, and the ipsilateral lead is introduced. This lead is also anchored to the retromastoid fascia. A subclavicular subcutaneous pocket is then prepared, and the leads are tunneled from the retromastoid incision to the pocket. The leads are then inserted into the pulse generator, and the pulse generator placed in the pocket. The pulse generator may be a primary cell or rechargeable.

Hardware Selection and Device Programming

We prefer the use of cylindrical percutaneous leads for both the trial and permanent implant – paddle leads are only used in rare cases of frequent lead migration. ONS, as a form of peripheral neurostimulation, stimulates the terminal branches of the nerve fibers and as such should be multidirectional, in contrast to spinal cord stimulation, where unidirectional stimulation of the spinal cord is preferable.

Programming of occipital nerve stimulators is fundamentally similar to spinal cord stimulator (SCS) programming. We have found that patients often times prefer higher pulse widths, as compared to SCS, which are also better tolerated as there are no unwanted neural elements (i.e., thoracic nerves roots) to be recruited. Unlike in SCS, it appears that ONS may be effective in some headache syndromes, i.e., cluster and migraine headache, even when the paresthesias do not fully cover the area of pain.

Complications

While the placement of an occipital nerve stimulator is a relatively safe procedure, postoperative complications, though at a relatively low rate, do occur [10]. In a retrospective analysis by Schwedt et al., 60 % of patients undergoing ONS for chronic headache required lead revision within 1 year [15]. Several complications have been

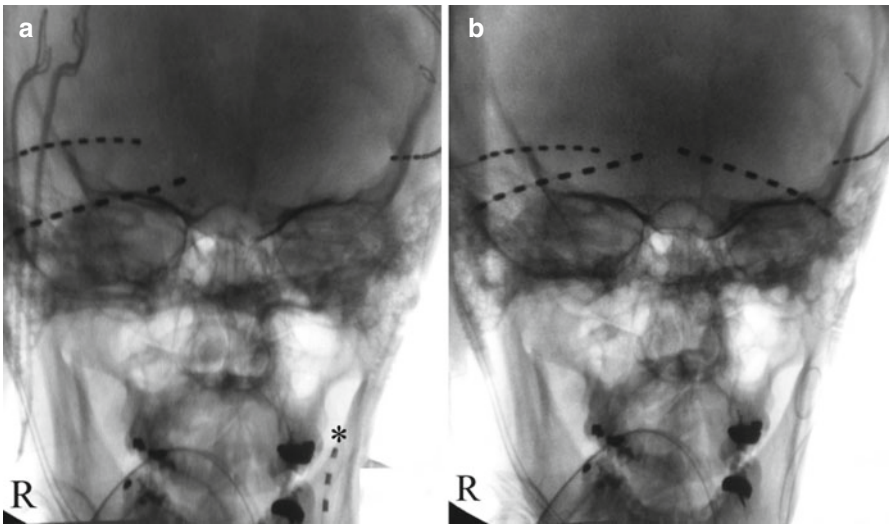

Fig. 4 Intraoperative AP radiograph demonstrating migration of left occipital lead (*) in a patient with migraine headaches (**a**). The left occipital lead was then replaced during revision surgery (**b**)

reported following ONS, including the following: lead migration, infection, wound erosion, device failure, muscle spasms, and pain [1, 19]. Most commonly, lead migration is associated with ONS [18, 19] (Fig. 4). Often lead migration may require surgical intervention. Schwedt et al. demonstrated lead migration rates of 33 % after 6 months, 60 % after 2 years, and 100 % after 3 years [15].

In the authors' experience, lead migration occurred in 7 % of patients. Infection necessitating explanation and replacement occurred in 8 % of patient, of which 50 % were upon initial implant and 50 % following surgical revision. All impending wound erosions were revised preemptively in order to prevent infection. None of the patients who were preemptively revised developed a wound erosion or infection. The overall rate of complications was 15 %. Revision surgery for a variety of other indications was performed in 22 % of implanted patients. Most of these cases were done on an elective basis for cosmetic reasons [10].

Corrective surgery may be performed using a distal to proximal lead revision technique. As previously described, this technique is designed to efficiently and safely adjust lead position via both lead depth and lead tip location [9]. Moreover, the revision technique may be carried out without a need for replacement of individual components or modification of the entire system. Gofeld described a technique of retrograde lead insertion after lead migration of an occipital neurostimulator [3].

Though many serious complications of ONS exist, preventative measures may help to reduce the incidence of complication such as infection and lead migration. As in all surgery, adherence to meticulous sterile surgical technique will help reduce the incidence of infection. We routinely perform preoperative skin testing via nasal swab for Methicillin-resistant *Staphylococcus aureus* (MRSA). Should MRSA colonization be a concern, preoperative antibiotic treatment in an attempt at decolonization should be employed prior to implantation, and vancomycin should be used prophylactically during the perioperative period. Prevention of lead migration can be accomplished by use of anchoring devices, although great care must be taken to place these anchors deep enough under the skin so as to prevent skin erosion at a later date.

Conclusion

ONS is a safe and efficacious treatment for a variety of headache disorders. Should medical therapy fail, patients may benefit from and should be encouraged towards ONS trials. The exact mechanism of action for peripheral neurostimulation is not concretely known, but most likely its effects are due to multiple mechanisms. While complications like lead migration do arise, perioperative preventative measures may help to reduce the incidence of such complication. Should complications like lead migration arise, novel approaches to corrective surgery have been thoroughly described in the literature.

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State-of-the-Art Endovascular Treatment of Acute Ischemic Stroke

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Abstract Stroke is the third leading cause of death in the USA. An estimated 795,000 new or recurrent stroke events occur annually, mostly ischemic in nature. Arterial recanalization and subsequent reperfusion performed shortly after symptom onset can help to restore brain function in acute ischemic stroke (AIS). The only treatment currently approved by the United States Food and Drug Administration is intravenous tissue plasminogen activator, administered within 4.5 h of symptom onset. However, this short window often precludes effective intervention. Mechanical neurothrombectomy devices offer many potential advantages over pharmacologic thrombolysis, including more rapid achievement of recanalization, enhanced efficacy in treating large-vessel occlusions, and a potentially lower risk of hemorrhagic events. The goal of this chapter is to describe the state-of-the-art neurothrombectomy devices and stenting techniques for endovascular treatment of acute ischemic stroke, as well as to highlight recent advances in reperfusion therapies. Ongoing clinical trials, some with randomized, controlled designs, are included.

Keywords Acute ischemic stroke • Endovascular • Intra-arterial thrombolysis • Interventional • Mechanical thrombectomy

Abbreviations

AIS	Acute ischemic stroke
ASPECTS	Alberta Stroke Program Early CT Score
BA	Basilar artery
CT	Computed tomography
ECASS	European Cooperative Acute Stroke Study
FDA	Food and Drug Administration
IAT	Intra-arterial thrombolysis
ICA	Internal carotid artery
IMS	Interventional Management of Stroke
INR	International normalized ratio
IVT	Intravenous thrombolysis
IV-tPA	Intravenous tissue plasminogen activator
MCA	Middle cerebral artery
MERCI	Mechanical Embolus Removal in Cerebral Ischemia

MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
pCR	Phenox clot retriever
PROACT	Prolapse in Acute Cerebral Thromboembolism
PS	Penumbra System
sICH	Symptomatic intracranial hemorrhage
TICI	Thrombolysis in Cerebral Ischemia
TIMI	Thrombolysis in Myocardial Infarction

Introduction

Stroke is the third leading cause of death and the most common disabling disease in the USA. An estimated 795,000 new or recurrent events of stroke occur annually, mostly ischemic in nature [5, 53]. The natural history and poor clinical outcome of acute ischemic stroke (AIS) have been well documented. In 1999, stroke was responsible for an estimated5.54 million deaths worldwide [16, 54].

The last decade has witnessed rapid advances in our understanding of the physiopathology and neuroimaging of cerebral ischemia [16]. The currently recommended therapy is intravenous tissue plasminogen activator (IV-tPA) to be administered close to the onset of symptoms [33, 42]. In a breakthrough randomized trial in 1995, The National Institute of Neurological Disorders and Stroke (NINDS) showed that IV administration of fibrin-specific agents was associated with both revascularization and clinical improvement in all subtypes of ischemic stroke. It also proved that the benefits of thrombolysis with tpA (alteplase) extend beyond 1 year after treatment [42]. The placebo-controlled European Cooperative Acute Stroke Study (ECASS III) reported that compared to controls, patients treated with IV tPA for AIS soon after symptom onset had a higher rate of excellent clinical outcome, defined as a score of 0 or 1 on the modified Rankin Scale (mRS) (52 vs. 45 %, $p=0.04$), with no significant between-group difference in mortality (17 % vs. 21 %, respectively), although symptomatic intracranial bleeding occurred more frequently in the tPA group (2.4 vs. 0.2 %, $p=0.001$). They suggested that a 3–4.5-h interval from symptom onset to tPA treatment was safe and effective. Thereafter, the American College of Chest Physicians (ACCP) extended their therapeutic window for tPA from 3 to 4.5 h [43] despite a lower level of evidence (grade 2C). Nevertheless, even the longer interval is often not sufficient to ensure timely and effective intervention.

Prompted by findings of the importance of early recanalization of the occluded cerebral vessel in improving outcome [5, 57, 70], researchers are addressing attention to mechanical thrombectomy devices [70, 82], used together with IV tPA or as an alternative when tPA is contraindicated. Potential advantages include a wider time window (up to 8 h) and high recanalization rates (up to 82 %) [19, 27]. However, randomized trials testing their clinical benefit against IV thrombolysis, the current

gold standard [19], are lacking, and such trials are becoming increasingly difficult to perform because of the rapid evolution of the multimodal approach and the constant introduction of new and improved devices. Furthermore, true clinical success depends not only on timely reperfusion but also on the appropriate degree of reperfusion: recanalization and reperfusion of ischemic tissue may occasionally exacerbate tissue damage by reperfusion injury, cerebral edema, and hemorrhagic transformation [16]. Therefore, to investigate the therapeutic value of mechanical thrombectomy devices in AIS, we conducted a comprehensive review of recent trials using mechanical endovascular therapy with and without thrombolysis.

Intra-arterial Thrombolysis

The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (which was published in 1999) was the first randomized controlled study to propose that acute stroke can be treated by an endovascular approach. All patients had middle cerebral artery (MCA) occlusions and were treated with intra-arterial (IA) prourokinase within 6 h of symptom onset [22]. Inclusion criteria were age 18–85 years and a National Institutes of Health Stroke Scale (NIHSS) score of 4 or more, except for isolated aphasia or hemianopsia. Compared to the control group, the treated group had significantly better vessel recanalization, defined as a Thrombolysis in Myocardial Infarction (TIMI) score of 2 or more (66 % vs. 18 %, $p<0.001$) and a more favorable outcome, defined as an mRS score of 2–3 (40 % vs. 25 %, $p=0.04$). Although the drug was not approved because of a lack of a second, confirmatory, trial, the intra-arterial approach (with prourokinase or tPA) began to be used worldwide for emergency treatment of patients presenting within 6 h of onset of AIS in a large proximal vessel, such as the internal carotid artery (ICA) or MCA or within 24 h of onset of acute basilar artery (BA) occlusion [1, 4, 15]. Factors found to be associated with good outcome were collateral flow, age younger than 60 years, and low NIHSS score [4, 16].

Combined Intravenous and Intra-arterial Thrombolysis

Combined thrombolysis begins with the IV route and proceeds to the IA route. This approach may be used as a “bridging” therapy, with immediate transition to IA administration after IV treatment, or as a rescue therapy, wherein IA treatment is administered only if the first (IV) intervention fails to restore flow [21].

Interventional Management of Stroke (IMS) Trials I and II

The randomized, multicenter Interventional Management of Stroke (IMS) trials I and II were designed to examine the recanalizing effect of combining IAT and IVT compared to IV tPA alone [16, 55, 87, 89]. Patients ($n=80$ and $n=81$, respectively)

were given a low dose of IV tPA (0.6 mg/kg) within 3 h of symptom onset, followed by treatment of any residual occlusion with up to 22 mg IA tPA, delivered at a rate of 10 mg/h. The IMS II trial was the first largest body of information regarding use of mechanical thrombectomy in conjunction with IV and IA thrombolytic use. In this trial, IV tPA, was administered within 3 h, followed by treatment of any residual occlusion IA tPA in combination with EKOS-delivered ultrasound in accessible vessels (EkoSonic Endovascular System, EKOS Corporation, Bothell, WA, USA), which was not systematically used. Previous evidence showed that ultrasound energy hastens clot breakdown [16, 56, 92]. Inclusion criteria in the IMS II trial were age 18–80 years and NIHSS score ≥10. TIMI 2–3 recanalization was achieved in 56 % of patients in the IMS I trial and 60 % in the IMS II trial; rates of symptomatic intracranial hemorrhage (sICH) were 6.3 and 9.9 %, respectively. A favorable outcome was documented in 55 % of patients in whom recanalization was achieved compared to 27 % of patients in whom it was not ($p=0.046$). The IMS II trial yielded better results than the NINDS rt-PA Stroke Trial [56], though the differences were not statistically significant: median treatment time, 140 min vs. 90 min; mortality rate, 16 % vs. 21 % despite the somewhat higher baseline NIHSS score of the selected IMS II population (19 vs. 17); mRS score ≤2, 46 % of patients vs. 39 %. The sICH rate at 36 h was 9.9 % in the IMS II trial, with 8.8 % of patients having more significant parenchymal hemorrhages, and 6.6 % in the NINDS trial. Patients with a score of more than 7 on the Alberta Stroke Program Early CT Score (ASPECTS), a semiquantitative scale of early ischemic changes on computed tomography (CT) [73], did particularly well (mRS score ≤2; 13 % effect size) with combined IV-IA thrombolysis compared to IV therapy alone [88], confirming the post hoc finding in the PROACT II study. The authors concluded that the combined IV-endovascular approach might optimize outcome and overcome the disadvantage of the IA route in terms of delay to treatment.

Sonothrombolectomy

Sonothrombolectomy with the special EkoSonic Endovascular system (EKOS Corp., Bothell, WA) was used in the IMS II trial, which provided the largest body of data to date on this method. The findings supported earlier clinical studies demonstrating the capability of ultrasound to hasten clot breakdown [16, 18, 56, 91, 92] and enhance enzymatic thrombolysis [64]. Specifically, ultrasound was found to increase the transport of tPA into the thrombus, promote the opening and cleaving of the fibrin polymers, and apparently improve the binding affinity of tPA to fibrin. Patients in the IMS II trial who received ultrasound treatment had higher rates of recanalization than those who did not.

Recently, researchers tested the combination of externally applied transcranial Doppler (TCD) monitoring and IA delivery of gaseous microspheres of augment thrombolysis [41]. A retrospective comparison study design was used. The sample group included 111 consecutive registry patients who had undergone IA thrombolysis over a 9-year period; 33 were aged 80 years or more, and 81 were older than 80. The two age groups were very similar in baseline characteristics, including

pretreatment stroke severity (NIHSS score 17 vs. 16), differing only in history of stroke/transient ischemic attack (42 % vs. 22 %, $p=0.01$) and weight (66.8 kg vs. 75.8 kg; $p=0.02$). There were no significant differences between the older and younger groups in rates of recanalization (TIMI 2–3; 79 % vs. 68 %, respectively, $p=0.10$), major sICH (7 % vs. 8 %), or any intracerebral hemorrhage (39 % vs. 37 %). The older group had significantly lower rates of excellent functional outcome, defined as mRS score ≤1 (26 % vs. 40 %, $p=0.02$) and survival (57 % vs. 80 %, $p=0.01$) [41].

Mechanical Thrombectomy Protocols

Mechanical thrombectomy was designed for application when failed IAT follows failed IVT [21] or when thrombolysis is contraindicated by bleeding diathesis, warfarin use, elevated international normalized ratio (INR), major surgery within the prior 14 days, thrombocytopenia, genitourinary or gastrointestinal bleeding, and associated trauma such as a fall at onset of stroke symptoms. Following the IMS trials, several studies found that a mechanical approach, used alone or in combination with IV and IA tPA, could improve the recanalization rate and, thereby, patient outcome [77, 78]. Mechanical thrombectomy has since become a key player in the field of endovascular therapy. Originally restricted in many centers, the technique has undergone rapid evolution, accompanied by the creation of new devices, many of which are already on the market.

In light of these events, and with consideration of the necessary learning curves, in 2008, Stead [84] conducted a meta-analysis of the use of mechanical thrombectomy in the treatment of ischemic stroke. A total of 114 studies of the early experience with the first devices were systematically reviewed. The results showed that a TIMI flow grade of 2 or 3 was obtained in 68.7 % of all patients and in 72 % of patients with accessible clots. TIMI grade 3 flow was restored in 45.6 %. Among patients with an accessible clot, 36 % had an mRS score of ≤2 and 29 % died; among patients with an inaccessible clot, 24 % had an mRS score of ≤2 and 38 % died. However, hemorrhage occurred in 22 % of patients. Compared with a matched cohort, patients who received mechanical intervention were 14.8 times more likely to have a good mRS score (95 % confidence interval 4.4–50.0, $p<0.001$). It seems that the best candidates for thrombectomy are patients with MCA occlusion treated with combined IV/IA thrombolysis.

RECANALISE Study

In the observational, single-center RECANALISE study (2009), Mazighi et al. [58] assessed the outcome of combined IV tPA and endovascular thrombectomy for AIS with proven (by magnetic resonance angiography or CT angiography) arterial

occlusion. This was the first study to compare patients treated with this approach to a control group treated with IV alteplase alone (the gold standard). During phase 1 (February 2002 to March 2007), the IV-tPA patient group was identified from a prospective clinical registry; during phase 2 (April 2007 to October 2008), patients treated with the IV-endovascular approach were prospectively enrolled in the study. Phase 1 patients received 0.9 mg/kg IV alteplase; phase 2 patients received 0.6 mg/kg IV alteplase which was followed by 0.3 mg/kg IA alteplase if catheterization performed immediately after IV treatment laboratory showed persistent arterial occlusion. If recanalization did not occur after IV and IA alteplase, additional mechanical procedures were done (4 mm snare [Goose Neck Snare, EV3] or balloon angioplasty [Maverick angioplasty balloon, Boston Scientific]). Neurological improvement was defined as an NIHSS score of 0 or 1 or a decrease of 4 points or more at 24 h after treatment. Recanalization was achieved in 87 % of the patients treated with the IV alteplase-endovascular approach compared to 52 % of the patients treated with IV alteplase alone (adjusted RR 1.49, 95 % CI 1.21–1.84, $p=0.0002$). Corresponding rates of early neurological improvement were 60 % and 39 % (adjusted RR 1.36, 05 % CI 0.97–1.91, $p=0.07$), and of favorable outcome (mRS $\leq$2 at 90 days), 57 % and 44 % (adjusted RR 1.16, 95 % CI 0.85–1.58, $p=0.35$). The mortality rate at 90 days was 17 % in both groups, and sICH was documented in 9 % and 11 % of patients, respectively. Recanalization rates were higher after IV-endovascular treatment independently of the site of the occlusion. Two patients had complications related to IA alteplase: subarachnoid hemorrhage after vessel perforation in one and local puncture hematoma in the other. Within the IV alteplase-endovascular group, a shorter time from symptom onset to recanalization was associated with better clinical outcome. Ninety-two percent of the patients in whom recanalization was achieved within 3.5 h had a favorable outcome, and for each 30 min lost, the probability of a favorable outcome decreased by 20 %.

Interventional Management of Stroke (IMS) Trial III

The IMS III efficacy trial, begun in 2007, sought to compare the IV approach with the IV/IA approach plus the use of ultrasound (EKOS) as well as the Concentric Merci retriever device, Penumbra system or Solitaire FR stent-retriever device. IMS III clinical trial was conducted in the USA and Canada, and enrollment stopped since April 2012 (NCT00359424) [3, 40]. Inclusion criteria were the same as for the IMS I and II; the planned total sample size was 900. Subjects were randomized in a 2:1 ratio to two groups receive the standard full dose of tPA (0.9 mg/kg, 90 mg maximum, with 10 % as bolus) over 1 h or a lower dose of IV tPA (~0.6 mg/kg, 60 mg maximum) over 40 min followed immediately by angiography. If no treatable thrombus was demonstrated, therapy was terminated. If angiography identified the thrombus, treatment was continued with a mechanical device followed by infusion of tPA and delivery of low-intensity ultrasound at the site of occlusion using the EKOS microinfusion or a standard microcatheter. The choice of IA strategy was

made by the treating neurointerventionalist. IA treatment had to begin within 5 h and be completed within 7 h of stroke onset [3, 40]. An interim analysis was conducted in May 2012 by the independent Data and Safety Monitoring Board based on the 3-month mRS results of 587 participants at over 50 sites in the USA and Canada. The findings showed that the study had a very low likelihood of demonstrating the prespecified, clinically significant difference in benefit between the treatment arms. Enrollment was therefore stopped. No serious safety concerns were identified.

Mechanical Thrombectomy Strategies

Mechanical thrombectomy devices can be divided into three groups by mode of use. Distal clot-retrieval devices were developed and implemented first, followed by proximal aspiration devices, and then endovascular by-pass devices.

Distal Clot Retrieval

The first mechanical thrombectomy devices were advanced through the clot and delivered to its distal part via a microcatheter; the clot was then retrieved by pulling on the device.

Mechanical Embolus Removal in Cerebral Ischemia (MERCI)

The MERCI (Concentric Medical, Mountain View, CA) was one of the first devices to be used in mechanical thrombectomy and is probably the most evaluated so far. It consists of a balloon-guided catheter and a flexible corkscrew-shaped nitinol (nickel titanium) retriever (Figs. 1 and 2) [23]. The balloon of the guiding catheter is inflated proximal to the clot to achieve flow arrest and prevent distal embolization. The retriever ensnares the clot which is removed by pulling the retriever back into the catheter. Finally, the occluding proximal balloon is deflated to restore circulation [7].

The efficacy of the device was tested in the MERCI phase I trial [23]. Part I included 30 patients attending seven centers in the USA. The main inclusion criteria were NIHSS score $\geq$10, endovascular treatment performed within 8 h of symptom onset, contraindication to IV tPA, no findings of large hypodensity on CT scan, and angiography-confirmed occlusion of a major cerebral artery. Safety was defined by the absence of vascular injury or sICH. Efficacy was assessed by recanalization rate and clinical outcome at 1 month. Significant recovery was defined as an mRS score of $\leq$2 at 30 days in patients with a baseline NIHSS score of 10–20 or an mRS score of $\leq$3 at 30 days in patients with a baseline NIHSS score of >20. The device was

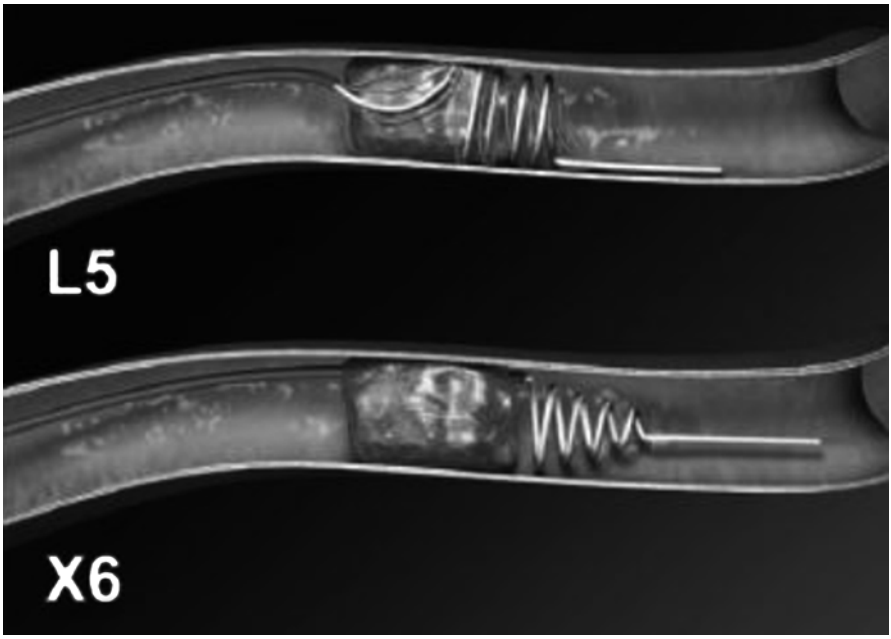


Fig. 1 MERCI Retriever. L5 device (*above*) and X6 device (*below*) engaging the clot (Courtesy of Concentric Medical, Inc.)

successfully deployed in 28 patients. Recanalization (TIMI 2 or 3) was achieved in 43 % of patients with mechanical embolectomy only, and in 64 % of patients with additional IA tPA. There was one procedure-related technical complication of no clinical consequence. Intracranial hemorrhage occurred in 12 patients, asymptomatic in all of them. At 1 month, 8 of 9 revascularized patients and 0 of 10 nonrevascularized patients achieved significant recovery.

Part 2 of the MERCI trial included 151 patients attending 26 centers in the USA, all with an INR of >3.0 [82]. The device was deployed in 141 patients. The recanalization rate was 53.5 %, and the favorable outcome rate (mRS ≤2 at 90 days) was 25 % [86]. The system received Food Drug Administration (FDA) approval in August 2005 [7].

The Multi-MERCI was an international multicenter single-arm trial with three objectives: to gain greater experience with the first-generation MERCI retrieval devices (X5 and X6) in patients ineligible for IV tPA; to investigate the safety and technical efficacy of the MERCI clot retriever in patients after failed IV tPA; and to collect safety and technical efficacy data on the second-generation L5 MERCI retriever [37, 81]. Inclusion criteria and techniques were otherwise similar to the MERCI I trial. The recanalization rate was 57.3 % with the L5 retriever alone (Fig. 2), and 69.5 % after adjunctive IA therapy based on angiography findings ($n = 131$). There was a 27 % absolute difference in mortality between patients who were or were not successfully recanalized.

Fig. 2 MERCI Retriever – the latest V-series (With permission from Concentric Medical)

Whereas the MERCI and Multi-MERCI trials were designed to study the MERCI embolectomy device in a trial context, with predetermined inclusion/exclusion criteria, the MERCI Registry study, initiated in June 2007, was an open-label prospective 36-center assessment of postmarketing real-world use of the MERCI retriever system in the interventional treatment of acute stroke. In 2010, an interim analysis of the registry period between June 2007 and December 2009 was performed (unpublished data) [36]. Of the 814 patients originally enrolled, procedural data were collected for 771 of whom 625 were included in the final cohort. (The others were lost to follow-up, missing data, or excluded because of a baseline mRS score of $\geq$2.) The findings were compared with the pooled MERCI/Multi-MERCI cohort of 305 patients. The MERCI Registry patients had a significantly lower baseline NIHSS score than the MERCI/Multi-MERCI patients (17.9 vs. 19.6, $p<0.0001$), with no significant difference in comorbidities or medical history. Compared to the MERCI/Multi-MERCI cohort, the MERCI Registry cohort had a significantly longer onset-to-puncture time (5.72 ± 3.28 h vs. 4.35 ± 1.76 h, $p<0.001$), lower percentage of patients who arrived less than 3 h from symptom onset (12.2 % vs. 20.8 %, $p=0.0008$), and higher percentage of patients treated beyond 8 h (14.1 % vs. 1.3 %,

$p<0.001$). There was no between-group difference in puncture-to-recanalization time (MERCI Registry, 1.92 h; MERCI/Multi-MERCI, 1.89 h) or occlusion site (ICA 31 %, MCA-M1 49–52 %; vertebrobasilar circulation 8.2–9.2 %). The MERCI Registry group had a significantly higher rate of adjuvant pharmacological thrombolysis (IV lytics 27.8 % vs. 15.7 %, $p<0.0001$; IA lytics 46.5 % vs. 31.8 %, $p<0.0001$); 6.9 % received glycoprotein IIb/IIIa antagonists. Good revascularization, defined by the Thrombolysis In Cerebral Ischemia (TICI) IIb-III, was documented in 52.2 % of patients, with the lowest favorable recanalization rate in the ICA (45.6 %) and the highest in the vertebrobasilar circulation (64.7 %). The overall recanalization rate was 77 % compared to 64.6 % in the MERCI/Multi-MERCI cohort ($p<0.0001$). There was no significant difference between the groups in favorable day-90 mRS score (≤2) or day-90 mortality (29–32 % vs. 34–38 %), or in rates of sICH, defined as a decrease of more than 4 points on the NIHSS (6.2 % vs. 8.8 %). The following results were found on multivariate analysis to identify predictors of good clinical outcome (mRS score ≤2 on day 90): baseline NIHSS score, OR 0.86 ($p<0.0001$); age, OR 0.96 ($p<0.0001$); revascularization, OR 2.97 ($p<0.0001$); intubated state during the procedure, OR 0.43 ($p=0.0004$).

It should be noted that the MERCI Registry study had several important limitations: nonrandomized cohort, nonmandatory consecutive enrollment, self-reported data, lack of a control group precluding comparisons with standard medical therapy, and lack of a core laboratory review. Nevertheless, it offers the largest prospective collection of data on mechanical embolectomy. In addition, using the registry, subsets previously too small for analysis could be analyzed, such as effect of intubation on outcome and time windows of treatment and procedure duration. The authors concluded that the real-world unconstrained experience with the MERCI embolectomy device for AIS yields similar clinical outcomes, safety data, and recanalization rates to those observed in previous trial studies. Successful recanalization was associated with higher rates of good clinical outcome [36].

Phenox Clot Retriever (pCR)

The pCR (Phenox GmbH, Bochum, Germany) is a more recent thrombectomy device designed specifically for intracranial clot removal. It has been available for use in Europe since 2006 [8]. The device is comprised of a dense array of soft perpendicular-oriented nylon fibers that gradually increase in length and attach to a flexible nitinol/platinum alloy compound core wire (Fig. 3). The fibers are resistant to unraveling and offer a high surface area for thrombus retrieval. The wire also carries proximal and distal visible X-ray markers for radio-opacity, facilitating handling and safety. The flexible design makes it possible for the surgeon to use two devices at once for bifurcations or larger vessels (kissing technique), and the microfilaments make it possible to lessen distal emboli owing to the filter effect. The device comes in three sizes measuring from 1 to 3 mm proximally and from 2 to 5 mm distally, for use in target vessels of ≥1, ≥, and ≥3 mm in diameter, respectively. It is shaped onto a 0.010-in. microguidewire and can be deployed using a

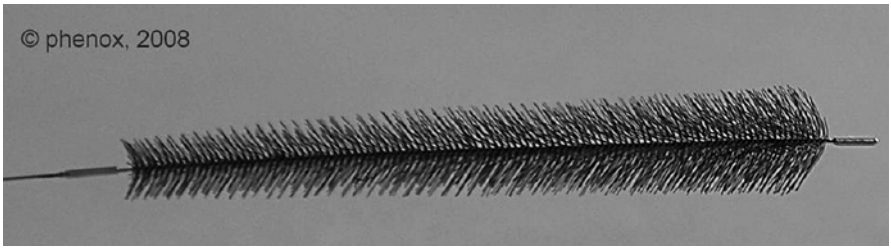


Fig. 3 Phenox clot retriever (pCR) (Courtesy of Phenox GmbH)

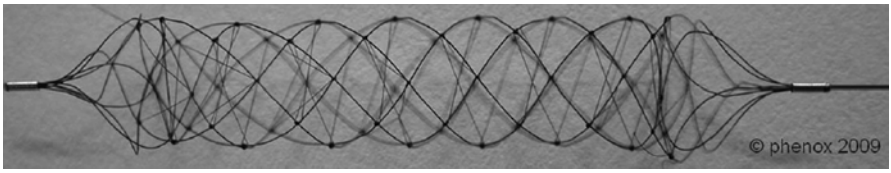


Fig. 4 Phenox clot retriever, BONnet device (Courtesy of Phenox GmbH)

standard microcatheter (0.021 or 0.027 in.). Animal experiments demonstrated that the device can be used for atraumatic retrieval of clots [65].

Another form of the pCR, known as the BONnet Intracranial flow Restoration Device (Fig. 4), consists of a nitinol braiding that self-expands into a cell-like structure to entrap the thrombus. Nylon filaments run through the braiding to provide additional surface area to keep the thrombus in place. Because of the braided design, the length of the device can be adapted to the vessel diameter [65]. The BONnet is positioned through a 0.021-in. microcatheter and deployed by pulling back on the microcatheter. After deployment, both the BONnet and microcatheter are slowly withdrawn under continuous aspiration into a guiding or aspiration catheter.

Only a few small clinical reports on the use of pCRs for AIS are available [34, 51, 52]. The first, published in 2006, described two successive patients who were ineligible for IV/IA thrombolysis. Endovascular recanalization was successfully achieved in both, with complete neurological recovery and no adverse events [34]. The second study, presented at the International Stroke Conference in 2008 [52], reported a subset analysis of 60 vascular territory applications of the pCR in 55 patients treated in three centers in Europe (Bonn, Munich, and Stuttgart) in 2007. Most target vessels had a diameter of $\leq$2 mm. The majority were reached and recanalized without difficulty. A total of 85 % of occluded vessels were recanalized with the pCR, yielding a 68 % overall recanalization rate with distal reperfusion. When the device was combined with IAT, the recanalization rate rose to almost 80 % (30/38). There were no device-related adverse events. However, three attempts failed because the device and/or microcatheter could not be deployed. A third small series of three children with AIS included one treated with the pCR for occlusion in the BA [28]. Partial recanalization was achieved, with no adverse effects.

Like for the MERCI retriever, randomized controlled trials of the pCR are needed to validate its use in clinical practice. The pCR holds promise as a useful supplement to the repertoire of currently available devices for endovascular thrombectomy [8].

Catch Device

The Catch (Balt Extrusion, Montmorency, France) is an intracerebral thromboembolectomy device developed in 2005 [6, 8]. It is comprised of a self-expanding nitinol braided basket and a Vasco+21 microcatheter equipped with a microguidewire (Fig. 5). The nitinol basket has a maximum diameter of 4 mm, which is suitable for clot retrieval in arteries up to 5 mm in diameter. A 6-Fr guide-catheter is recommended for use in conjunction with the device. The manufacturer has recently developed a mechanical thrombectomy kit consisting of a Balt Corail 8F+LT50 guide-catheter with occlusion balloon and distal extension for aspiration, a Balt Vasco+35ASPI microcatheter for proximal aspiration, and the Balt basket-like Catch device for clot retrieval. The Catch is deployed distal to the thrombus by retracting the microcatheter. The whole device is pulled back to withdraw the clot down to the guide-catheter, thereby reducing the risk of clot fragmentation. If further attempts to retrieve the clot are required, the resheathing hub included in the package may be used. Two in vivo animal studies have been conducted in Switzerland to evaluate the efficacy and potential complications of the Catch compared with the MERCI retriever [8, 11]. Both devices were used in 10 vessel occlusions: 4 in the ICA and 6 in the lingual artery (a branch of the external carotid artery). Seventy percent of the occlusions were successfully recanalized (TIMI grade 2–3) with the Catch device and 90 % with the MERCI retriever. The MERCI retriever was far superior in achieving recanalization at the first attempt (OR 21, 95 % Cl 1.78–248.11), such that significantly more attempts were made with the Catch device ($n=14$; $P=0.02$). Recanalization also took more time with the Catch device (average 20 min vs. 13 min). The Catch device caused more thrombus fragmentation during retrieval (OR 15.6. 95 % Cl 1.73–140.84) and more distal thromboembolic events. No dissections or perforations were reported, although the incidence of vasospasm was similarly high for both systems (average ate=3). The authors concluded that both the Catch device and the MERCI retriever are effective for mechanical thrombectomy in patients with AIS, but the MERCI retriever is better. To account for the problem of loss of thrombus material, although not explicitly recommended by the manufacturer, the authors suggested that the Catch device be used with balloon occlusion and aspiration.

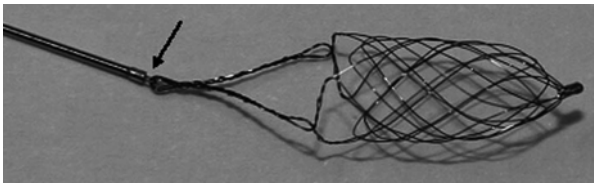


Fig. 5 Basket-like Catch device. Once deployed, the Catch device cannot be pulled back into the microcatheter (*arrow*) (Courtesy of BALT Extrusion)

Comparative Studies

A comparative in vitro study [8, 51] evaluated the effectiveness of five mechanical thrombectomy devices in thrombus retrieval and the risk of distal embolization for each: Catch (Balt), MERCI (Concentric), In Time and Attracter (Boston Scientific), and pCR (Phenox). Distal dislocation and retrieval of the thrombus was achieved with all devices at the first passage, although with markedly different rates of thrombus fragmentation and distal embolization. The MERCI, Catch, and pCR devices successfully removed the entire clot from the test tube, but the In Time and Attracter devices removed only part of the clot.

Despite encouraging results from the few studies that have been conducted thus far, it is clear that further research, particularly in the form of randomized trials, may provide compelling evidence as to the clinical effectiveness of endovascular treatment with the Catch device [8].

Proximal Clot Aspiration

Some thromboembolectomy devices are designed for use from the proximal to the distal part of the clot. Most of then used aspiration methods (Penumbra Device) or ultrasound (EKOS system). Since we already mentioned the EKOS on the IMS studies discussion, we complete the information of this group with the penumbra device.

Penumbra Aspiration System

The Penumbra Aspiration system (Penumbra Inc., Alameda, CA) is designed to remove intracranial occlusions by debulking, aspiration, and extraction [24]. It is comprised of an aspiration platform containing multiple devices that are size matched to the specific neurovascular anatomy (Fig. 6). A 2.8–5 F reperfusion catheter is connected to the aspiration pump, generating a suction force of −700 mmHg. Because the device works on the proximal surface of the occlusion, it optimizes safety and eliminates the need for navigation beyond the clot. Early clinical experience suggests that the Penumbra can be applied for successful revascularization in patients with acute stroke [24]. In an early study, Grunwald et al. [28] used the Penumbra to treat two of three patients aged 7–16 years with AIS; the remaining child was treated with the pCR. Partial recanalization was achieved with no adverse events. This prompted a larger, prospective, single-arm trial by the same group [29] including 23 patients with angiographically verified occlusion of a treatable intracranial vessel who presented within 8 h of symptom onset. Twenty-one target vessels in 20 patients were treated with the Penumbra system. All were revascularized to TIMI grade 2 or 3 (100 % success rate). At the 30-day follow-up, 45 % of patients showed an increase of 4 or more points on the NIHSS or an mRS score of $\leq$2.

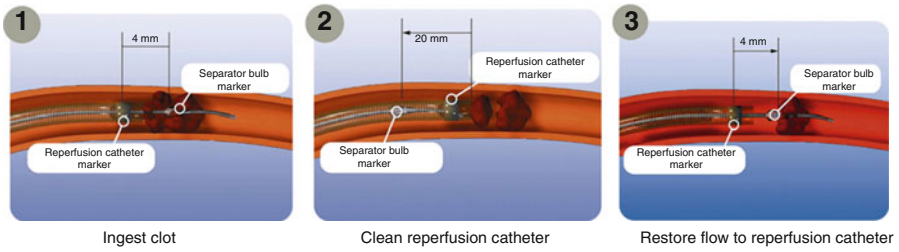


Fig. 6 Penumbra Aspiration System. During manipulation, the separator should completely exit the catheter and be withdrawn completely into the catheter (Courtesy of Penumbra Inc.)

The mortality rate was 45 %, which was considered good in this cohort in which 70 % of patients had a baseline NIHSS score of >20 or BA occlusion [9]. The Penumbra was approved by the FDA in 2008.

The same year, Bose et al. [9], from the University of Saarland, reported the results of a 3-year prospective, nonrandomized, single-center controlled study of the clinical and functional outcome of 29 patients with stroke in the posterior circulation, including acute occlusions of the distal ICA (T-lesion), MCA–M1, or BA. Mechanical thrombectomy with the Penumbra was applied in patients who were ineligible for IV tpA or failed IV tPA administered within 3 h of symptom onset. Mean baseline NIHSS score was 20 for the whole cohort and 33.5 in the patients with BA strokes. Complete revascularization (TIMI 3) was achieved in 72.4 % of patients, and partial revascularization (TIMI 2) in 13.8 %. Revascularization failed in 13.8 %. The subgroup with BA strokes had a partial revascularization rate of 83.3 %. The NIHSS score improved by 4 points or more in 65.5 % of the cohort, and an mRS score of ≤2 was documented in 37.9 %. There were no device-related adverse events. Seven percent of patients had sICH [9].

Results of the Penumbra Pivotal Stroke Trial [71] were presented at the International Stroke Conference in February 2008 and published shortly thereafter. A prospective, multicenter, single-arm, nonrandomized design was used. The sample consisted of 125 patients with neurological deficits (NIHSS ≥8) at presentation and angiographically proven occlusion (TIMI 0 or 1) of a treatable large intracranial vessel (total, 125 target vessels). Patients were either ineligible for or refractory to tPA therapy or presented beyond the 3-h window (between 3 and 8 h of symptom onset). At 90 days after treatment, revascularization was successful (TIMI 2–3) in 81.6 % of treated vessels. Eighteen intraprocedural events were reported in 16 patients (12.8 %); in 3 patients (2.4 %), the events were considered serious. Intracranial hemorrhage was detected on 24-h CT scan in 35 patients (28 %), of whom 14 (11.2 %) were symptomatic. All-cause mortality was 32.8 % at 90 days, with 25 % of patients achieving an mRS score of ≤2. The authors concluded that the Penumbra is safe and effective for revascularization in patients with AIS secondary to large-vessel occlusive disease if administered within 8 h of symptom onset. Although the primary endpoint was met, this study was criticized for the low rate of 90-day functional independence. Goyal et al. [25] attempted to explain

the enigma of the high revascularization rate on the one hand and lower-than-expected good-outcome rate on the other. Analysis of the pretreatment CT scans revealed that an ASPECTS score of >7 (small infarct) at baseline was associated with a higher likelihood of achieving functional independence after revascularization than a score of ≤7 (50 % vs. 15 %; $p=0.0001$), and a total of 64 % of patients in the trial presented with large infarcts. This finding, along with other emerging data [95], supports the use of advanced imaging selection to guide the use of IA therapy.

Thereafter, 7 international centers published their collective post-marketing experience with the Penumbra Aspiration System in a retrospective review of 157 consecutive patients (Penumbra POST) [86]. Mean patient age at baseline was 65 years, and mean NIHSS score, 16. The rate of MCA occlusions (58 %) was lower than in the Pivotal trial, and the rate of vertebral artery occlusions (20 %) was higher, but neither of these differences was statistically significant ($p<0.05$). Revascularization was documented in 87 % of the treated vessels: to TIMI 2 in 54 % and to TIMI 3 in 33 %, compared to 82 % in the Pivotal trial. In addition, 32 % of patients received adjunctive IA lytic treatment during the procedure, 18.5 % received IV lytic treatment prior to the procedure (refractory to tPA), and 23 % received both. Although the IA tPA group tended to have a higher rate of sICH, adjunctive lytic therapy did not materially affect the revascularization rate or the clinical outcome. There were 9 serious procedural events (5.7 %): 2 dissections, 2 perforations, one access site hematoma, one peripheral hemorrhage, and one cardiac arrest. Three device malfunctions occurred, including 2 fractures of the 032 reperfusion catheter at ~40 cm from the tip, and one breakage of the 041 separator at ~6 mm from the distal end of the device. The breakage was due to a hard clot that required the operator to pull back on the separator with considerable force after penetrating the thrombus. The tip of the separator stayed within the thrombus and was not retrievable. None of these malfunctions led to a serious adverse event or patient death. The all-cause mortality rate was 20 %. Forty-one percent of patients had an mRS score of ≤2 at 90 days compared to 25 % in the Pivotal trial. Although the postmarketing Penumbra data were not significantly different from the Pivotal trial data, the proportion of patients with a good functional outcome was higher than expected. A review of the Penumbra POST trial database did not reveal a definitive reason for the observed difference in outcome between the studies. However, it raised the intriguing possibility that it was at least partly attributable to an inherent variability in patient stroke pathophysiology at presentation.

The 2011 Penumbra SPEED study [20] assessed the safety and efficiency of the 054 catheter, which was added to the existing 3 catheters of the Penumbra system in 2009. It features a larger, 0.064 in., proximal internal diameter for enhanced aspiration efficiency. The interim results ($n=73$) yielded a median aspiration time of 18 min compared with 45 min for the original catheters used in the Penumbra Pivotal trial ($p<0.001$). The time from puncture to final revascularization was 53.5 min in the SPEED study and 97 min in the Pivotal Trial. The 054 catheter was associated with a high revascularization rate (TIMI 2–3) of 92 % when used as frontline therapy, prior to any adjunctive treatment.

Endovascular Bypass: Stentrievers

The use of stent retrievers (stentrievers) in AIS is based on the rationale that temporary endovascular bypass allows for rapid flow restoration. During stent deployment, the thrombus is displaced and entrapped between the stent and the vessel wall, and a channel is created inside the thrombus. No anticoagulation is needed as the stent can be recaptured without subsequent antiaggregation [83]. The literature on stent-assisted recanalization in AIS has been accumulating in the last few years. The first report on the deployment of a stent across a thrombus in AIS appeared in 2006 [10]. The first stent used in this context was the Enterprise (Cordis, Miami Lakes, FL).

Solitaire Self-Expanding Stent

The Solitaire (ev3 Inc., Plymouth, MN) is a self-expanding stent initially designed for stent-assisted coiling in remodeling of brain aneurysms (Fig. 7). It is currently offered in two versions: aneurysm bridging (AB) and flow restoration (FR). The Solitaire is unique in that it can be fully deployed and then completely retrieved if not detached [35, 87] once recanalization is established. Although detachment of the device is not within the primary scope for the treatment of ischemic stroke, it is a viable option if thrombectomy fails and thrombus compression by the deployed stent restores flow in the target vessel [72]. Other advantages include a closed-cell

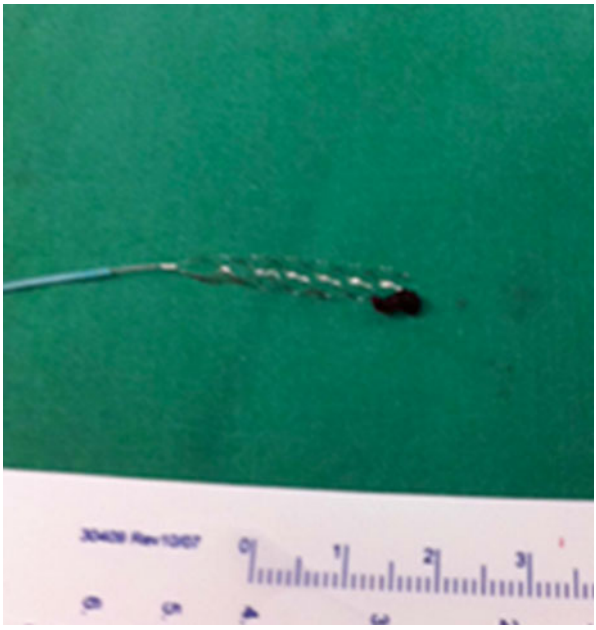


Fig. 7 Solitaire stentriever with a retrieved clot

design, high comparative radial force, high cell deformation resistance, and good vessel-wall adaptation. Furthermore, the device is applicable multiple times and can be used even in small peripheral vessel branches (e.g., M2 segments). The FR variant was CE-marked for mechanical thrombectomy in July 2009.

The results of the first (pilot) study of the Solitaire AB stent in mechanical thrombectomy were published in 2010 in *Stroke*. Castaño et al. [12] prospectively evaluated the intraprocedural and postprocedural findings in 20 patients with large artery occlusions of the anterior circulation attending a single tertiary center. All were refractory to or ineligible for IV tPA. Additional inclusion criteria were age ≤80 years, NIHSS score ≥8 (or lower if there was a fluctuating neurological deficit), <8 h between symptom onset and presentation, absence of large signs of ischemia (defined as an ASPECT score of <7 or magnetic resonance diffusion-weighted lesion in >50 % of the MCA territory), and proven occlusion of the anterior circulation on angiography. The treatable vessels included the terminus ICA, tandem proximal ICA/MCA, and MCA-M1 and -M2. The median NIHSS score was 19 (interquartile range, 15–23). An 8-Fr balloon guide-catheter was inserted via a femoral approach, so that the device was positioned in the proximal ICA. A heparinized saline solution was continuously perfused through the catheter during the procedure. With the balloon of the guide-catheter deflated, a 0.014-in. guide wire was advanced coaxially over a Rebar 18 microcatheter (ev3 Inc., Irvine, CA) within the occluded intracranial vessel and navigated distal to the clot. The microcatheter was then advanced over the wire through the clot, and the guide-wire was exchanged for the Solitaire AB embolectomy device. The device was advanced and deployed, with its distal portion placed a few millimeters distal to the clot. If the clot was shorter than the stent (20 mm), flow distal to the thrombus was restored immediately. The stent was maintained in place for 1 or 2 min, followed by inflation of the guiding catheter balloon to arrest the flow. The microcatheter and embolectomy device were gently aspirated simultaneously through the guiding catheter. Successful revascularization, defined as TICI 2b/3, was achieved in 90 % of treated vessels; flow was immediately restored in 80 %. The mean number of passes for maximal recanalization was 1.4, and the median (quartiles) time from groin puncture to recanalization was 50 min (range 38–71 min). In no case was adjuvant therapy required after deployment of the embolectomy device. There were no significant adverse procedural events. Distal embolization to the MCA territory occurred in two patients, but there were no cases of thrombus migration to a different territory. There were also no cases of arterial rupture or dissection. Two patients (10 %) had sICH: one fatal parenchymal hemorrhage, and one subarachnoid hemorrhage. Four patients (20 %) died during the 90-day follow-up period. Forty-five percent of patients showed a good functional outcome at 3 months (mRS ≤2). Age and NIHSS score were predictors of good outcome, in agreement with other reports on thrombectomy [82, 84]. The mean number of passes was lower than in the MERCI studies (2.9 passes), and the mean time from groin puncture to recanalization was shorter. This study suggested for the first time that the Solitaire AB device can rapidly, safely, and effectively retrieve clots from the MCA terminus and ICA within 8 h of symptom onset.

In other small case series, Miteff et al. [61] evaluated 26 consecutive patients, Nayak et al. [67] 7 patients, and Möhlenbruch et al. [63] 25 patients. Recanalization (TIMI grade ≥2) was achieved with Solitaire thrombectomy as monotherapy in 61.5, 100, and 88 % of patients, respectively. Corresponding rates of sICH were 7.7, 0, and 12 %. In the series of Miteff et al. [61], a favorable clinical outcome (mRS ≤2) was documented in 3 of 5 patients (79 %) with MCA occlusion, 6 of 11 patients (55 %) with ICA occlusion, and 2 of 10 (20 %) with BA occlusion; in the series of Nayak et al. [67], an improvement of more than 4 points on the NIHSS was documented in 5 patients (20 %), of whom 4 (57 %) had a 30-day mRS score of ≤2. No data on clinical outcome were available for the series of Möhlenbruch et al. [63]. Additional single-center experiences with the Solitaire for AIS are summarized in Table 1.

The two most comprehensive series of temporary endovascular bypass with the Solitaire were those of Liebig et al. [50] (50 patients and 53 occlusions) and Costalat et al. [17] in the Rescue, Combined Management and Stand-Alone Thrombectomy (RECOST) study (100 patients and 103 large-vessel occlusions). In the study of Liebig et al. [50], repeated stent manipulation was required in 64 % of patients; only six procedures (11 %) resulted in stent deployment. There were four adverse events, none device related. Immediate reperfusion (TICI ≥2a) was achieved in 73.6 % of procedures, extending the theory that stenting leads to relatively quick recanalization. The final reperfusion (TICI 2–3) rate was 86.6 %. The RECOST study used three different thrombectomy strategies based on time of symptom onset and location of vessel occlusion (MCA-M1 or -M2, 40 % of patients; ICA, 28 %; BA, 32 %). (1) Rescue therapy (24 % of cases) was applied in patients with MCA-M1 or -M2 occlusion who presented within 4.5 h of symptom onset and failed early IV tPA treatment (defined as NIHSS ≥8 60 min after IV fibrinolysis or neurological deficit significantly impacting quality of life). (2) Combined (bridging) therapy (56 % of cases) was used in patients with terminal ICA or tandem occlusions who presented within 4.5 h of symptom onset and patients with BA occlusions who presented within 24 h. No second neurological assessment was obtained before urgent thrombectomy, and IV fibrinolysis was continued during the endovascular procedure. (3) Stand-alone thrombectomy (20 % of cases) was used in patients who presented beyond the IV fibrinolysis therapeutic window (4.5–6 h for MCA and terminal ICA occlusions) and patients with well-accepted contraindications to IV fibrinolysis. Mean patient age was 67.6 years. All patients underwent clinical and magnetic resonance imaging (MRI) assessment. Mean NIHSS score at presentation was 14.7, and mean MRI ASPECT score was 6. Mean recanalization time from symptom onset was 377 min, with an overall recanalization rate (TICI 3) of 84 %. NIHSS score at discharge was 6.5; 60 % of patients had an NIHSS score of 0–1 or an improvement of >9 points. The symptomatic complication rate was 10 %. At 3 months, 54 % of patients had mRS score ≤2; the overall mortality rate was 12 %. The authors concluded that patient selection by MRI ASPECT score contributed to the low complication rates because it prevented futile and dangerous interventions [17].

The preliminary results of the ongoing Solitaire FR With the Intention For Thrombectomy (SWIFT) Study [80], the first to compare the Solitaire self-expanding

Table 1 Additional one-center experience published studies of the Solitaire stent-retriever device for acute ischemic stroke

Author, year (Ref.)	n	Onset-to-recanalization (mean, hours)	Baseline NIHSS (median)	Device + Adjuvants[a]	Good recanalization (TIMI IIb/III) (%)	No. of attempts (mean)	mRS ≤ 2 (day 90)	Mortality	sICH
Mpostsaris, 2012 [66]	26	5.27	16	19/26 (73 %)	69	1	10 (38 %)	2 (7.7 %)	NA
Cohen, 2012 [15]	17	45 min[b]	20	–	100	2	15[c] (88.2 %)	1 (5.8 %)	2 (11.8 %)
Menon, 2012 [60]	14	84 min[b]	NA	9/14 (64.3 %)	85.7	1–5	8 (57 %)	2 (14.3 %)	4[d] (28 %)
Wehrschuetz, 2011 [94]	11	5.6	16	11/11 (100 %)	100	2.3	3 (30 %)	1 (9 %)	0
Stampfl, 2011 [83]	18	4.8	21 (Mean)	17/18 (94.4 %)	88.8	2.5	6 (33 %)	5 (2.7 %)	3 (16 %)
Roth, 2010 [77]	22	4.6	19	13/22 (59 %)	90.9	1 (40 %)	11 (50 %)	4 (18.1 %)	2 (18 %)

NA not available, *NIHSS* National Institutes of Health Stroke Scale, *TIMI* Thrombolysis In Myocardial Infarction, *mRS* modified Rankin Scale, *sICH* symptomatic intracranial hemorrhage

[a]Including IV lytics

[b]Puncture to recanalization

[c]At 1 month

[d]Overall sICH rate

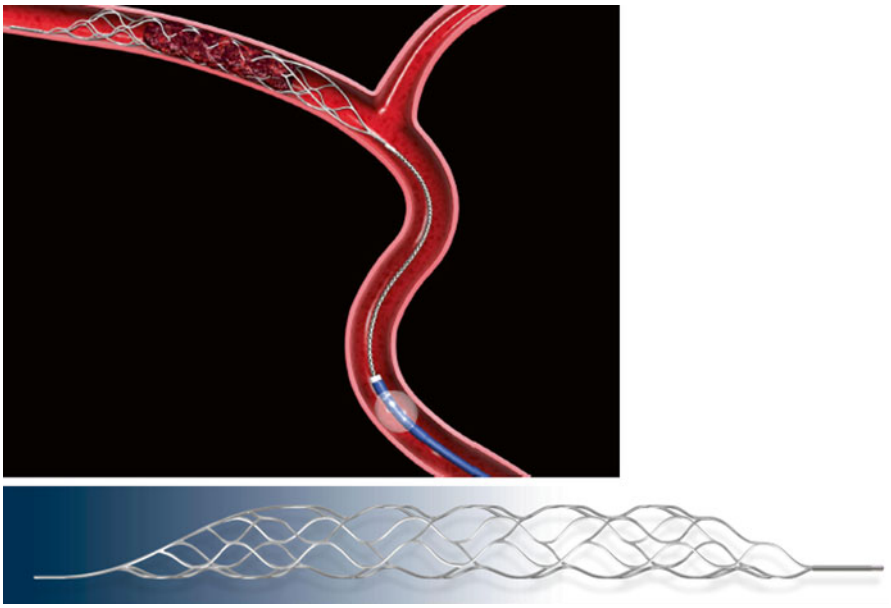
stent with the MERCI retriever as initial therapy, were reported in 2012 at the International Stroke Conference. A multicenter, randomized, active comparator, noninferiority study design was used. Between January 2010 and December 2011, 58 patients were randomized to the Solitaire FR arm, and 55 to the MERCI arm. Primary endpoints were successful recanalization (TIMI 2 or 3 in all treated vessels), no sICH, and no rescue therapy (tPA, IIb/IIIa antagonists, etc.). Secondary endpoints were either good clinical outcome (mRS ≤ 2 or equal to the prestroke mRS if the prestroke mRS was higher than 2 or improvement by ≥ 10 in NIHSS score). A core lab blinded to the treatment assignment provided independent angiographic, CT, and MRI evaluations. Compared to the MERCI arm, the Solitaire FR arm had significantly higher rates of successful recanalization without sICH (core-lab-assessed) (60.7 % vs. 24.1 %, $p=0.0001$), end-of-procedure successful recanalization (core-lab-assessed) (80.4 % vs. 57.4 %, $p=0.013$), and good neurological outcome (mRS ≤ 2 or improvement in NIHSS score by ≥ 10) at 90 days (58.2 % vs. 33.3 %, $p=0.017$), and a significantly lower 90-day mortality rate (17.2 % vs. 38.2 %, $p=0.02$).

The sponsored multicenter prospective Solitaire FR Thrombectomy for Acute Revascularization (STAR) study [26] is the first "real-life" investigation of use of the Solitaire for acute stroke. The enrollment of 206 patients from 18 centers in Canada and Australia has just been completed. Inclusion criteria are presentation within 8 h of symptom onset and contraindications for IV tPA or failed IV tPA after bridging therapy or thrombectomy as initial treatment.

A search of PubMed until December 2012 using the combined keywords "Solitaire" and "stroke" yielded 43 publications of related devices to the Solitaire system. Early followers are discussed below, including the Trevo (Concentric Medical), the ReVive (Micrus Endovascular), and the Aperio (Acandis). Others include the IRIIS Plu and OptiCell (MindFrame, CA), the Pulse (Penumbra), and the pREset (Phenox) [72]. They differ in several features, but their intended clinical use is essentially similar.

Trevo Device

The Trevo (Concentric Medical Inc., Mountain View, CA) is designed for mechanical removal of occlusive thrombi in vessels ranging from 1.5 to 3.5 mm in diameter [59]. It measures 44 mm in length and 4 mm in diameter and has a hydrophilic coating to reduce friction during use. The device consists of a 180-cm long, proximal 0.018-in. core wire, with a 75-cm transition area at the proximal end and a closed-cell stent-like section at the distal end (Figs. 8 and 9). The proximal 10 mm are tapered for easy resheathing, and the distal 10 mm are tapered for smooth transition from the tip to the active area of the device. The distal tip is soft and floppy for safe and accurate deployment, and radiopaque to facilitate fluoroscopic visualization. The higher radial force across the active area allows for placement of the device in more distal and smaller vessels and more efficient clot retrieval and incorporation. A shaft marker indicates the proximity of the device to the microcatheter tip. By contrast to stents used to treat intracranial aneurysms (neck bridging) or



Figs. 8 and 9 Trevo stentriever (Courtesy of Concentric Medical Inc.)

intracranial atherosclerosis, in which the broader portion of the struts is in contact with the blood vessel wall in order to optimize coverage and wall apposition, in the Trevo device, the broader portion of the struts has an endoluminal orientation to optimize thrombus incorporation.

Nogueira et al. [69] recently published their preclinical experience with the Trevo device in confirmatory animal models (2 swine, 1 canine) of arterial thrombo-occlusive disease induced by autologous thrombin-generated thrombi. Device performance was evaluated by angiographic response and clot incorporation by the device; high-resolution flat-panel three-dimensional CT was performed to further define the in vivo device-thrombus-vessel interaction. In addition, samples from vessels treated with 6 passes of the device were explanted for histopathological analysis. Sixteen clots of variable hardness and consistency were retrieved from the internal maxillary, lingual, and forelimb arteries (swine models) as well as from the external carotid and vertebral arteries (canine model). TIMI 2–3 reperfusion was achieved in all cases immediately after device deployment. One pass was required for 15 clots and 2 passes for the remaining clot. Histopathological analysis demonstrated severe disruption of the intima but no hemorrhage of the media or adventitia. The authors concluded that the Trevo device is highly effective at achieving immediate reperfusion of occluded arteries without causing any clinically significant disruption of vascular integrity.

Mendonça et al. [59] recently conducted the first prospective in vivo study of the safety and effectiveness of the Trevo device, used alone or combined with IA thrombectomy within 8 h of symptom onset. Clinical, radiological, and functional

data were collected for 13 patients with an angiographically verified occlusion of the anterior cerebral circulation. Median baseline NIHSS score was 19 (range 16–22). The MCA was occluded in 8 patients and the ICA in 5. Revascularization was achieved in 77 %. The mean time from groin puncture to recanalization was 95 ± 31 min. No significant intraprocedural complications occurred. Four patients (30 %) died within 90 days of the procedure, and 4 patients (30 %) achieved functional independence. One or two passes were usually sufficient to achieve recanalization (61 %), similar to rates for other retrievers [12, 84].

Another prospective, single-center study evaluated the role of the Trevo device as a primary intention-to-treat tool in patients with stroke of <8 h duration in the anterior circulation ($n = 54$) or <12 h duration in the vertebrobasilar circulation ($n = 6$) [79]. Mean patient age was 71.3 years. In all cases, CT perfusion/CT angiography confirmed a large-artery occlusion or showed target mismatch (if the time from symptoms was >4.5 h) and ruled out a malignant profile. The median (interquartile range) NIHSS score on admission was 18 (range 12–22), and the median time from stroke onset to groin puncture was 210 min (range 173–296 min). Successful revascularization was achieved in 73.3 % of cases with Trevo monotherapy and in 86.7 % with combination therapy with other devices or IA tPA. The median duration of the procedure was 80 min (range 45–114 min). A good outcome (mRS ≤2) was achieved in 45 % of patients. The mortality rate was 28.3 %. Seven patients (11.7 %) had sICH (parenchymal hematoma type 1 or 2 and increase of 4 or more points on the NIHSS). No other major complications were detected.

The final results of the prospective single-arm Thrombectomy REvascularization of large Vessel Occlusions (TREVO) in acute ischemic stroke study were presented at the 2012 International Stroke Conference [90]. Sixty patients from seven centers in Germany, Spain, Austria, and Sweden were included. All underwent primary monotherapy with the Trevo device. The primary endpoint was revascularization, assessed by an independent core lab (at UCLA, Los Angeles, CA); secondary endpoints were mRS score at 90 days, mortality at 90 days, device-related serious adverse events, and sICH within 24 h. Median patient age was 65 years (range 21–84 years); median baseline NIHSS score was 18 (range 8–28). The ICA was occluded in 21.7 % of cases, the MCA in 70 % (M1 segment, 60 %), and the vertebrobasilar (VB) in 8.3 %. Mean time from symptom onset to puncture was 3.5 ± 1.4 h (≤3 h in 46.7 %; 4.5–8 h in 23.3 %). IV lytics were administered before intervention in 60 % of patients. Final TIMI 2b-3 recanalization was achieved in 78.3 % of occluded vessels (estimated preintervention TIMI 0, 95 %). Intracranial hemorrhage occurred in 30.0 % of patients: asymptomatic in 25.0 %, symptomatic in 5 % (defined by the Safe Implementation of Thrombolysis in Stroke MOnitoring STudy – SITS-MOST [93]), and device-related (perforation) in 5 %. The median NIHSS score was 9.5 in the first 24 h (47 % reduction from baseline) and 2 at 90 days (89 % reduction from baseline). Fifty-five percent of patients had a favorable 90-day clinical outcome (mRS 0–2). Although this was not a randomized study, the results were very encouraging, suggesting that the Trevo device could be a welcome addition to the interventional arsenal against acute stroke, offering neurointerventional experts another option when addressing difficult embolectomy procedures [90].

Revive Device

The Revive system (FAST Self-Expanding Basket Thrombectomy Device, Micrus Endovascular, San Jose, CA) is a new, European-made CE-marked stentriever for intracranial thrombectomy [75]. It consists of a closed basket instead of a coil to enhance clot removal (Fig. 10). The deployed stent has a length of 22 mm and a maximum diameter of 4.5 mm, and it can be delivered through a 0.021-in. microcatheter. The struts in the Revive are 25 % taller than in the Solitaire FR and 7 % taller than in the Trevo, providing the Revive with more surface area to encapsulate the clot. Furthermore, the Revive is 31 % thinner than the Solitaire FR so it can better penetrate and enmesh thrombus formations. Other features include small midbasket cells (which also increase surface area), helical cell pattern, high number of cells, and consistent radial force designed to retain the clot inside the retriever, not outside against the vessel.

Rhode et al. [75] conducted the first and so far only clinical study of the Revive. The sample included ten patients of mean age 78.3 ± 6 years treated for AIS in October 2010 to December 2010. At admission, mean NIHSS score was 19.0, and mean duration of symptoms, 172 min. Bridging IV thrombectomy was started within 4.5 h for MCA occlusions ($n = 4$) and 6 h for terminal ICA or BA occlusions

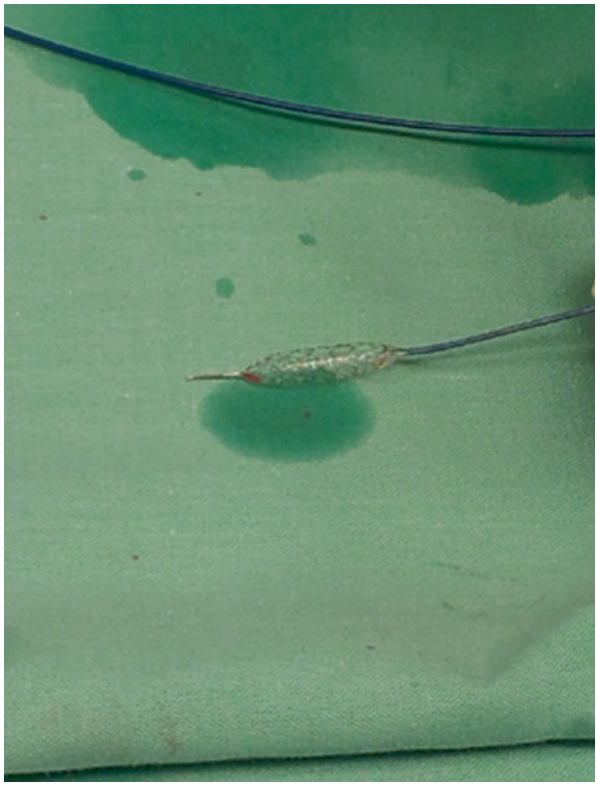


Fig. 10 Revive stentriever with a retrieved clot

($n=5$), according to internal treatment guidelines. Mean number of passes was 3.0 ± 2.7 (range 1 to >10; >10 passes were needed in 2 cases of terminal carotid T-occlusion). Additional IA lyses were performed in 2 patients. Intravenous glycoprotein IIb/IIIa antagonist was administered to 2 patients in whom thrombectomy was prolonged (>5 passes) and 1 patient with high-grade ICA stenosis in whom stenting was required to gain access to an M1-2 occlusion. Patients received no heparin. All procedures were performed under general anesthesia. No endovascular tools other than the Revive device were applied. Interventions were started at a mean of 94 min from admission (range 34–150 min). Mean time from onset to complete recanalization was 88.7 ± 53 min (median 63.5 min). Recanalization (TIMI 2b or 3) was successful in all patients, with no device-related complications. Mean NIHSS score was 14.0 (range 0–42) at 24 h after the intervention, 11.5 (range 0–34) on day 30, and 5.1 (range 0–12) at discharge. On day 30, 6 patients had a clinical improvement of >8 points on the NIHSS ($n=4$) or an NIHSS score of 0–1 ($n=2$). One patient had minor clinical improvement, and 3 patients died, 2 of stroke (1 reperfusion bleeding, 1 brain stem infarction), and 1 of complicated pneumonia despite good neurological recovery. Two patients had a complete territorial infarction. On follow-up imaging, minor cerebral ischemia was noted in 7 patients, and no ischemia in one patient. Two patients had sICH. Complete recanalization was achieved in all patients, and favorable clinical outcome in 60 %. This was remarkable considering the advanced age of the patients, the severity of the stroke, and the high percentage of long segment occlusions (mean length of the occluded vessel segment 19.7 ± 13.4 mm, 60 % $\geq$10 mm). The recanalization rates were higher than those reported in the Penumbra Pivotal (81.6 %) and MERCI trials (69.5 %) [71, 84], and in the recent study of Castaño et al. [12] using the Solitaire stent. The improved results are presumably a consequence of the closed-basket design of the Revive stent.

Aperio Device

The Aperio is a self-expanding nitinol laser-cut stent-like thrombectomy device. It has a hybrid design of small closed cells to optimize vessel adaption and wider, partially open, clot-catching cells, with markers to indicate device expansion and the proximal and distal wire [76]. The clot-catching cells contain an anchoring element for optimal clot fixation in tortuous vessels. The Aperio has a diameter of 4.5 mm and a length of 40 mm, and is intended for use in vessels ranging from 2 to 4 mm in diameter. The sole study of the Aperio in the literature to date was conducted by Roth et al. [76] who compared it for safety and efficacy with the Solitaire AB in a swine model. Selective vessel occlusion was induced by autologous blood clot injection in the subclavian or carotid vasculature within a 2- to 4-mm size range. Angiograms were analyzed by 2 experienced neuroradiologists who were blinded to the devices used. The Aperio was applied in 23 procedures and the Solitaire AB/FR (Aneurysm Bridging/Flow Restoration) in 18. Both devices allowed for very good fluoroscopic visibility, unfolded well after deployment, and

achieved 100 % recanalization of the target vessel (average TIMI score 2.8 for the Aperio and 2.7 for the Solitaire). These rates were higher than previously reported in clinical studies, although the vessels in the animal model were less tortuous and less elongated, with no atherosclerotic changes. There were no cases of device-related acute thrombosis, vessel dissection, or vessel perforation. Distal embolization occurred in 8 % of the Aperio procedures and 11 % of the Solitaire AB procedures; corresponding rates of device-related vasospasm were 9 % and 6 %. To achieve a TIMI score of ≥2, a mean of 1.4 runs was needed with the Aperio device and 1.2 runs with the Solitaire.

Comparative Ongoing Studies

An ongoing study, The Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE), will compare IV thrombectomy alone with combined IV and mechanical thrombectomy initiated within 4 h of AIS onset in patients with large artery occlusions and an NIHSS score of >10. The following devices will be used: the MERCI retriever, Penumbra Aspiration System, Trevo device, Catch device, and the Solitaire self-expanding stent. The trial is designed to test hypothesis that there is an overall absolute difference of 15 % in favorable outcome (mRS ≤2) for patients treated with the combined approach as compared with those treated with IV thrombolyses. Mechanical thrombectomy must begin within 5 h and be completed within 6 h of stroke onset. Trial enrollment began in the end of 2010. Up to September 2012, 203 patients were included. The planned sample size is 480 patients in 30 French sites [36].

Several other randomized clinical trials of endovascular reperfusion therapy are currently in progress or in the planning stage. These are summarized in Table 2.

Other Mechanical Techniques: Angioplasty and Permanent Stenting

Balloon angioplasty with intracranial stent placement has been used in the past for recanalization of cerebral arteries [13, 48, 49]. The main potential advantages of stent technology for AIS are a higher rate of recanalization and more rapid recanalization. Stents may be of particular value in patients with underlying intracranial atherosclerotic lesions or focal recalcitrant clots [24]. However, this technique has raised safety concerns because antiplatelet medications are required after the procedure to avoid acute stent thrombosis. Other risks include long-term restenosis in patients with a permanently implanted device and permanent side branch and perforator occlusion due to the compressed thrombus [16]. Self-expanding stents are usually preferred over balloon-mounted stents.

The preliminary data on self-expanding stents were limited to case reports and small case series. Gupta et al. [32] presented their initial experience with

Table 2 Ongoing randomized clinical trials (RCTs) of endovascular reperfusion therapy in acute ischemic stroke

Name	Therapy	RIVER III	THRACE	Mr CLEAN	PISTE
Trial driver/initiator	Company-driven		Government funded		
	Penumbra	Codman	French	Netherlands	UK
Principal investigator	J. Mocco	NA	S. Bracard X. Ducrocq	C. Majoie	K. Muir P. White
Devices	Penumbra	Revive	Solitaire	EVT	All CE marked for EVT stroke
			Merci		
			Catch		
			Trevo		
			Penumbra		
Current status	Ongoing since Dec 2011	Planned	Ongoing since Dec 2010	Ongoing since Dec 2010	Planned
Hypothesis	Superiority 12 %	Superiority 20 %	Superiority 15 %	Superiority 10 %	Superiority 15 %
No. of centers	15	30	27	11	12–15 (Only in UK)
No. of patients required/enrolled	692	258	480/203	500/106	400

EVT endovascular treatment, *NA* nonavailable

endovascular revascularization in 18 patients of mean age 66 years, with impending anterior or posterior circulation stroke (total 21 intracranial atherosclerotic stenoses) who failed medical management. TIMI grade 2–3 recanalization was achieved in 20 arteries, and only one patient remained at grade TIMI 0. However, 50 % of patients had major complications, including ischemic stroke in 2 (11 %) and sICH in 3 (17 %). Three patients (17 %) died. Interestingly, most complications were seen in patients with MCA involvement.

In another series, emergency angioplasty and stenting were performed together with IAT in 25 patients with ICA occlusion and secondary artery-to-artery embolism to the MCA [68]. Endovascular treatment was associated with higher rates of a favorable outcome than medical treatment (56 % vs. 26 %). Jovin et al. [38] achieved recanalization in 23 of 25 patients (92 %) by emergent stenting of the extracranial portion of the ICA. Two clinically insignificant adverse events were noted: asymptomatic hemorrhage and no flow-limiting dissection (one patient each).

Angioplasty with or without stenting has been successfully combined with emergency administration of thrombolytic agents in patients with occlusions in the VB circulation, Lin et al. [53] used a combined approach of proximal arterial stent placement followed by thrombolysis at variable times after symptom onset (range, 30 h to 5 days) in five patients with stroke of BA origin. An additional patient underwent carotid and subclavian stent placement plus BA revascularization. Good recanalization results were achieved in four of the six patients. Four patients had an excellent immediate recovery and were discharged to an acute rehabilitation unit or their homes with improved neurologic symptoms and functional status. Two

patients died: one who presented with coma and a baseline NIHSS of 38, and one who probably had a reocclusion of the BA within 24 h despite initial postprocedural improvement.

Other series reported reperfusion rates of approximately 80 % and mortality of about 30 %. Poor prognostic markers in the anterior circulation were lesion at the ICA terminus, older age, and higher baseline NIHSS score; poor prognostic markers in the posterior circulation were older age, diabetes, and long lesion [14, 16, 96, 97]. Levy et al. [47] reported a 79 % recanalization rate in 18 patients (mean NIHSS = 18) using self-expanding stent placement accompanied by various other endovascular techniques. A moderate clinical outcome (mRS ≤3 at 90 days) was achieved in 33.3 %. Brekenfeld et al. [10] treated 12 patients with AIS (mean NIHSS 14) using self-expanding stents; 7 had failed IA or mechanical thrombectomy, or both. Successful recanalization was achieved in 92 % of cases. A moderate clinical outcome was documented in 50 %. There were no cases of sICH.

A more recent retrospective study evaluated the feasibility, efficacy, and safety of intracranial artery recanalization using emergent angioplasty and stent placement without thrombolysis [30]. Eleven patients with acute MCA occlusion were included. Digital subtraction angiography revealed partial or complete recanalization (TIMI 2–3) in all cases immediately after stenting. One patient died of MCA reocclusion 2 days after the procedure. Among the survivors, 7 (70 %) had a good outcome (mRS = 0–2) and 3 (30 %), a moderate outcome (mRS = 3). Follow-up CTA or MRA revealed mild restenosis in 2 of the 10 patients. This preliminary experience demonstrates the technical feasibility and high rate of recanalization with emergent angioplasty and stenting without thrombolysis in patients with acute MCA occlusion.

In a case series reported in 2012, Sung et al. [85] evaluated the feasibility, efficacy, and safety of recanalization with the Wingspan stent (Boston Scientific, Freemont, CA) in 10 patients with acute MCA occlusion who failed or were ineligible for standard IVT or who presented more than 3 h after symptom onset. Mean NIHSS score at admission was 12.7 (range 4–21). In all cases, the stent was placed within 8 h of symptom onset: in the M1 segment of the MCA in 7 patients, and in the M2 segment, in 3. Successful recanalization was achieved in all patients. The mean interval from symptom onset to stent placement was 344.8 ± 76.3 min. There were no cases of intracranial hemorrhage, vessel perforation, or dissection. Nine patients showed an improvement in NIHSS score at 7 days. The remaining patient showed no change in NIHSS score even though the occluded artery was completely recanalized. At 7 days, the mean NIHSS score of all patients was 4.4 ± 4.7 (median 4, range 0–13). At discharge, an mRS score of ≤3 was documented in all patients, and mRS ≤2 was achieved in 7 patients (70 %).

Lee et al. [44] presented their single-center experience with 12 consecutive cases of acute MCA stroke in which balloon-expandable stent placement was performed for immediate reocclusion following IA thrombectomy. The median NIHSS score on admission was 8.6. Four patients received also IV tPA. The median time from symptom onset to IA thrombectomy was 236 min, and the median duration of IA thrombectomy was 62 min. The median dose of urokinase was 140,000 units. Initial

recanalization after stent deployment (TIMI 2–3) was achieved in all patients. Two patients died in hospital of aspiration pneumonia during medical management. In 2 patients, in-stent reocclusion occurred within 48 h of stent deployment. At discharge, the median NIHSS score in 10 patients (including those with re-obstruction) was 2.4. Eight patients had an excellent 3-month outcome (mRS 0–1).

A recent retrospective "real-world" study sought to determine predictors of recanalization during IA thrombectomy in 1,122 patients with occlusion of the anterior circulation from 13 stroke centers [31]. All underwent IA therapy within 8 h of symptom onset. Mean age was 67 ± 16 years, and median NIHSS score was 17. Half the patients had MCA-MI occlusions, 19 % carotid terminus occlusions, 15 % MCA-M2 occlusions, 13 % tandem occlusions, and 3 % extracranial ICA occlusions. Interventions included pharmacologic therapy in 24 %, mechanical therapy in 24 %, and multimodal therapy in 52 % (mechanical device in conjunction with a thrombolytic agent administered IV or IA). A total of 138 intracranial stents were placed, mainly after treatment failure: 96 stents (70 %) were deployed in the setting of multimodal therapy and 42 (30 %) as primary therapy. Intracranial stenting was associated with an 80 % recanalization rate when used as part of multimodal therapy compared to 71 % when used as primary therapy; the difference as not statistically significant. Patients treated with multimodal therapy had a significantly higher rate of TIMI 2–3 recanalization (74 %) than patients treated only pharmacologically (61 %) or mechanically (63 %) ($p \leq 0.001$). On binary logistic regression modeling, independent predictors of TIMI 2–3 recanalization were IA thrombectomy (OR 1.5, 95 % CI 1.21–2.08; $p \leq 0.001$) and stent deployment (OR 1.91, 95 % CI1.23–2.96; $p \leq 0.001$). The majority of patients in the current series underwent intracranial stent placement after failure of other treatment modalities.

The Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial [45] was the first FDA-approved prospective study to analyze the effectiveness of stenting in the treatment of AIS. It included 20 patients with mean NIHSS score of 14 treated within 6 h of symptom onset. In all cases, the target vessel was successfully recanalized. Adjuvant therapies were applied in 63.2 % of patients and included angioplasty, IAT, and IV tPA. Angiography yielded a TICI 2–3 flow in all patients. Moderate clinical outcome (mRS ≤3) was documented in 60 % of patients at one month and 6 months.

Conclusions

Endovascular reperfusion is a viable alternative for the treatment of ischemic stroke due to large vessel occlusion. However, endovascular approaches require dedicated stroke interventionalists with a support team of angiography technicians and nurses, as well as expensive equipment. Furthermore, patient selection is crucial. The intervention needs to be administered within a specific window of time from symptom onset, and it carries a risk of hemorrhage. For these reasons, many groups support the use of mechanical thrombectomy for more effective and rapid recanalization of

large occluded vessels. This work reviews several thrombectomy devices that have been introduced to the market and other promising novel approaches.

The initial results with the mechanical devices are encouraging. However, their clinical value in terms of improving outcome after AIS remains unproven. Further prospective randomized controlled trials are needed to determine the place of mechanical thrombectomy in stroke management, with a focus on ways to properly identify patients who will benefit most. In most cases, use of one device alone is sufficient to achieve recanalization. However, in a minority of patients, application of different catheters, several devices, or stent- and drug-device combinations may be required. The decision-making flow chart used in our institution for endovascular reperfusion therapy in AIS is shown in Table 3.

In summary, improving the safety, efficacy and accessibility to reperfusion therapies in AIS poses a great challenge. Several strategies are currently underway including development of new thrombolytic agents, multimodal reperfusion therapy, and rescue reperfusion therapy.

Proposals for the Future

Although IV thrombolysis was perceived as a very aggressive approach to acute stroke more than 15 years ago, neurologists have since learned that even more aggressive treatments may be warranted. If their efficacy is proven in clinical trials, the treatment of stroke will follow the road taken by cardiology years ago. Trials can be expected to involve several therapeutic pathways (1) evolutionary interventional techniques and new mechanical devices, used alone or in combination with tPA; (2) new pharmacologic agents, administered alone or in combination with tPA; (3) use of imaging to individualize the therapeutic window for both systemic therapy and IA interventions; and (4) new advances in the field of neuroprotection. In the interim, further efforts must be extended to get patients to hospitals early enough to offer IV and/or IA thrombectomy [74], including effective educational strategies to increase stroke awareness among the general population.

Disclosure The authors have no potential conflicts of interest relevant to this chapter.

Table 3 A proposed decision-making flow chart concerning endovascular reperfusion therapy in acute ischemic stroke

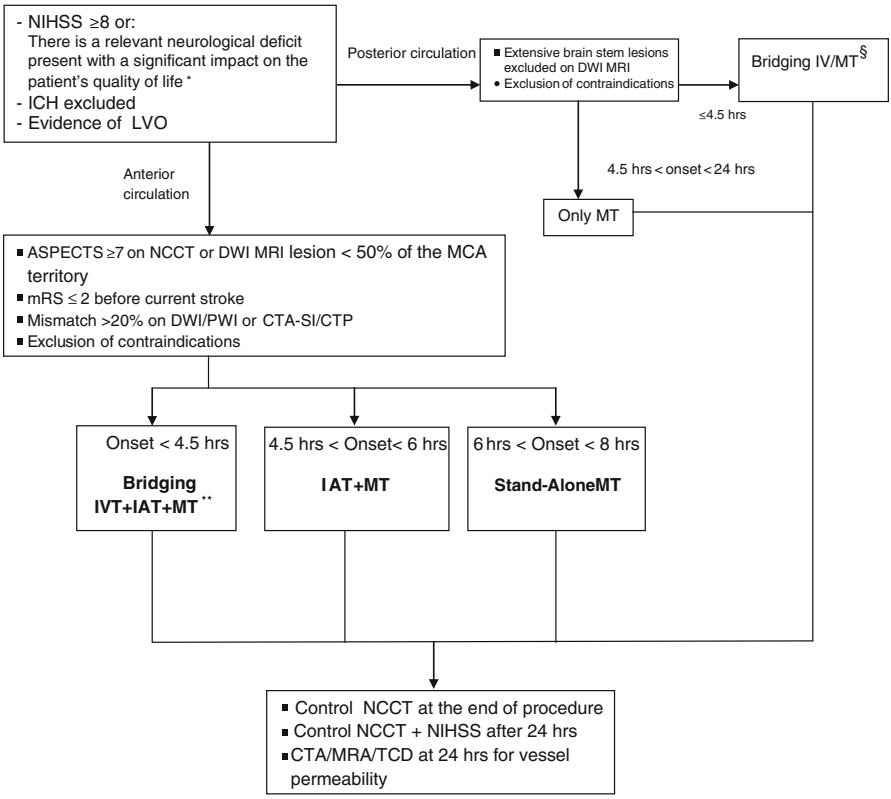
NIHSS National Institutes of Health Stroke scale, *LVO* large vessel occlusion (M1-M2 MCA, ICA or BA), *ICH* intracranial hemorrhage, *DWI MRI* Diffusion-Weighted Imaging MRI, *ASPECTS* Alberta Stroke Program Early CT Score, *NCCT* noncontrast CT, *MT* mechanical thrombectomy, *CTA-SI* CT angiography Source Imaging, *CTP* CT perfusion, *CTA* CT angiography, *MRA* MR angiography, *TCD* transcranial Doppler, *MT* mechanical thrombectomy, *IVT* IV thrombolysis, *IAT* IA thrombolysis

[a]Initial low dose IV tPA treatment (0.6 mg/kg) given during 40 min combined with mechanical thrombectomy +/− IAT

[b]Pregnancy, serum glucose <50 and >400 mg/dL; known hemorrhagic diathesis; known coagulation factor deficiency; oral anticoagulation treatment with international normalized ratio >1.5; use of heparin with a prothrombin time >2-times normal; platelet count <100,000/ml; sustained systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg despite treatment; and life expectancy <3 months

[c]Such as aphasia, hemianopsia or neglect

[d]Except in case INR > 1.5 – only MT will be applied



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Is There a Place for Microsurgical Vascular Decompression of the Brainstem for Apparent Essential Blood Hypertension? A Review

Marc Sindou

Contents

Abstract There are anatomical and physiological evidences that the ventrolateral (VL) region of the medulla plays an important role in blood pressure regulation and that dysfunction at this level may generate hypertension (HT). Vascular compression by a megadolicho-artery from the vertebrobasilar arterial system at the root entry/exit zone (REZ) of the glossopharyngeal (IXth) and vagal (Xth) cranial nerves (CNs) and the adjacent VL aspect of the medulla has been postulated as a causal factor for HT from neurogenic origin. The first attempts at microvascular decompression (MVD) of the IX–Xth CNs together with the neighbouring VL brainstem was revealed promising. These surgical attempts, as well as the numerous MRI studies, with the goal to detect and identify likely responsible neurovascular conflicts (NVC), are reviewed. Established criteria for indication of MVD as an aetiological treatment of apparent essential HT are still needed.

Keywords Brainstem compression • Essential hypertension • Microvascular decompression • Glossopharyngeal and vagal cranial nerves

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Introduction

Hypertension (HT) is a worldwide major problem that causes 7.1 million premature deaths and represents 4.5 % of the disease burden, namely, 64 million disability-adjusted life years (DALYs) according to the WHO International Society of Hypertension Writing Group [61]. Primary (in other words essential) HT is applied to the 95 % of cases in whom no specific aetiology can be identified. Because not all essential HT cases can be controlled by medications, the search for identifying eventual causative factors, among those is neurogenic dysfunction, is most justified. Among various factors responsible for neurogenic dysfunction, one cause may be vascular compression by an ectatic megadolicho-artery located at the rostro-ventro-lateral aspect of the medulla, especially on the left side, as postulated by Jannetta and his group in the late 1970s [27, 48].

Since then only few studies, either clinical [20, 28, 30, 33, 34, 39] or experimental [48–50], were reported in the literature, despite that such a neurogenic mechanism might potentially concern a large number of patients. As a matter of fact, there are robust anatomical/physiological evidences that compression of the IX–Xth root entry/exit zone (REZ) and adjacent rostro-ventro-lateral (RVL) medulla can be at the origin of systemic HT [2, 3, 8, 9, 11, 15, 18, 22, 24, 43, 45].

Anatomical–Physiological Bases

The anatomical and physiological background for such a hypothesis started more than a century ago when the medulla oblongata was recognized vital for cardiovascular function after Dittmar in 1873 observed a dramatic fall of blood pressure by transection of the brainstem caudal to the pontomedullary junction [18]. Later on, in 1946, the crucial role in blood pressure regulation of the sympathetic centres of the medulla was evidenced by Alexander who succeeded in obtaining a tonic effect on blood pressure by stimulating the medullary ventrolateral area [2]. Then, in the 1960s and 1970s, the presence of monoaminergic neurons was identified in the brainstem [15, 24], as well as the existence of bulbospinal projections to the intermediolateral cell column [3]. Soon after, in the 1980s, the localization in the RVL medulla of vasopressor neurons involved in arterial pressure control, namely, cell bodies containing adrenaline/noradrenaline, was demonstrated [4, 6, 16, 26, 43, 44]. Also, strong links were evidenced from the RVL medulla to the nucleus tractus solitarii [11, 45], as well as direct projections of the cardiovascular inputs entering the VL medulla onto the central autonomic area of the thoracic cord [8, 9].

Lesioning of the epinephrine neurons in the VL medulla was shown abolishing the vasodepressor components of the baroreflex and the cardiopulmonary reflex [22]. Meanwhile, experiments in baboons were performed by the group of Jannetta to induce arterial hypertension by mimicking neurovascular pulsating compression in the VL medulla; authors used a pulsatile inflated balloon device [48–50]. Haemodynamic changes were observed after pulsatile compression is performed on the left side, but not on the right side [49].

The First Surgical Attempts

The first clinical report on vascular compression as an aetiology of essential HT was by Jannetta and Gendell in 1979 [27]. They observed a high rate of neurovascular compression of the VL medulla on the left side in their patients affected with trigeminal neuralgia or hemifacial spasm when there was an associated hypertension, compared to the patients who did not have HT. Since then only two surgical studies were published: one retrospective, by Jannetta et al. [28], and one prospective, by Geiger et al. [20]. In Jannetta et al's series, of the 53 patients with essential HT, 51 had vascular compression at the left VL medulla. Among the 36 patients who benefited from a decompression considered "adequate", 32 (i.e. 89 %) had subsequent blood pressure normalization. In Geiger et al's series, of the 10 patients followed from 5 to 66 months, 8 (80 %) were improved, 3 of them requiring no further antihypertensive medications. Improvement in blood pressure occurred more often in the patients who underwent surgery on the left side [20, 28, 33, 39]. The predominant left-sided lateralization of blood pressure control is concordant with the prevalence of the left IX–Xth nerve complex in conveying the afferences originating from the baroreceptors of the (left-sided) cardiac atrium.

MRI Studies

Because all patients affected with essential HT not medically controlled cannot be candidates for surgical operation, a large number of studies were launched to evaluate the validity of MRI exploration to find out *neurovascular conflicts* (NVC) susceptible to cause the disease. Over the past 10 years, as many as 15 studies were carried out to assess the eventual role of a vascular compression at the brainstem in the genesis of HT [1, 10, 12, 21, 25, 29, 36–38, 40, 46, 51, 56, 58, 59, 62]. Of the 12 publications with detailed information, a majority (nine) reported a higher rate of images of vascular contact/compression (vc/c) at the VL medulla in the group of patients with essential HT, compared to the group of patients with normal blood pressure [1, 21, 25, 29, 36–38, 46, 51]. Also, of the ten publications providing information on the side of the compression, in six a higher rate of left-sided vc/c over right-sided vc/c was found in the essential HT group [1, 37, 38, 40, 46, 51, 58]. Further, in a recently published meta-analysis, including 597 patients with apparent essential hypertension and 609 controls, left-sided NVC at the VL medulla was prevalent in patients with essential HT. However, there was no significance when subanalysis was confined to the prospective studies – $p = 0.178$ for prospective vs. $p = 0.001$ for retrospective studies [7]. Thus, predictive value of MR imaging for selecting patients remains uncertain.

A major limitation for MRI screening is the difficulty to discriminate whether a detected elongated arterial loop in relation with the VL medulla and the adjacent IXth–Xth REZ is the cause or the consequence of the raised blood pressure. To address this problem several authors compared imaging findings between patients with apparent primary HT and patients with secondary HT [1, 21, 36, 37, 40, 46, 58].

Studies showed that in the group of patients with secondary HT, rate of NVC at the brainstem was less than in the group of patients with primary, i.e. essential, HT ($p=0.01$). In addition when an image of the megadolicho-artery was present, the vascular image was not predominantly left sided. However, these studies did not allow any definitive conclusion, due to the fact that the number of patients enrolled was not sufficient to reach statistical significance [7].

The Model, Hemifacial Spasm Associated with HT

Lack of reliability of MR screening to ascertain responsibility of neurovascular images in the genesis of HT makes it difficult to indicate vascular decompressive surgery in patients solely affected with apparent essential HT. Therefore, it has been considered wise to proceed through indirect ways to investigate the potential effect of MVD on pharmacoresistant HT, namely, investigating patients referred for HFS and having associated HT, as initially explored by Jannetta and Gendell [27].

In an ongoing study, we are assessing the effects obtained on blood pressure (BP) by vascular decompression of the IX–Xth REZ and adjacent VL aspect of the medulla (in addition to MVD of the facial REZ) in a group of 48 patients operated on for their hemifacial spasm (HSF) and who presented with an associated apparent essential HT. These 48 patients represented 23.88 % of the 201 patients who were referred for surgery of their HFS, over the past 20 years. Long-term effect of the MVD on patients' HT is at present under investigation. At first look, effect is promising; once statistical study will be completed, results will be submitted for publication.

Decompression of the IXth–Xth REZ and adjacent VL medulla, in addition to decompression of the facial REZ, does not require much more extensive surgical approach than the classical one for HFS [5, 35, 42, 47, 52, 53]. High-resolution MR imaging with special sequences allows to identify NVC with very high sensibility and specificity [31, 32, 54, 55].

Whether such an indirect approach is valuable to bring insight to knowledge must be questioned at first. Is the percentage of patients affected with HT associated with HFS higher than the one in the general population of same range of age? Whilst some publications report a higher prevalence of HT in patients with HFS than in control groups [17, 41], as high as in 67 % in the later publication, others did not find any statistically significant differences: Colosimo et al., 47.3 % vs. 52.7 % [13, 14], and Tan et al., 42.7 % vs. 39.1 % [57]. Discrepancy between these studies might be bias in the publications; studies with prevalence were of retrospective nature and/or were lacking of proper matching with controls.

An important study is the one by Nakamura et al., which brings convincing arguments for the role of vascular compression in the genesis of HT in patients with left-sided HFS harbouring NVC image at MRI exploration [38]. In this study there was no significant difference in prevalence of HT between the patients with HFS (82 patients enrolled) and the control group without HFS (similarly 82 patients enrolled, with age and sex matched), 39 % vs. 29.3 % ($p=0.19$); there was also

no difference between the patients with left-sided ($n=44$) and right-sided ($n=38$) HFS, 32 % vs. 47 %. Conversely, difference was significant when side and presence or absence of HT were considered together. As a matter of fact, a vascular compression at the VL medulla was observed at MRI in 86 % of the patients with left HFS who had HT ($n=14$) vs. in only 33 % of the patients with left HFS but without HT ($n=30$) ($p=0.0012$). To be mentioned, there was no such significance in patients with right HFS ($p=0.18$). Authors concluded that these findings are of clinical importance, at least for the patients who harbour left HFS and HT and perhaps also for those with sole essential HT provided that MRI shows vascular compression at the brainstem.

Conclusion

Arguments to estimate that vascular compression of the brainstem, particularly at the level of the IX–Xth REZ and adjacent VL medulla, seem robust enough to authorize neurosurgical community to consider surgical vascular decompression for treatment of apparent essential HT likely to be from neurogenic origin.

The main problem remains patients' selection. MR images of vascular contact/compression can well be the consequence of the elevated blood pressure, as well as the cause or a favourizing factor of the HT disease. In spite of the high number of studies, the problem is not already solved.

However, in patients in whom medical treatment is not able to control the blood pressure [19, 23, 60, 61], it could be justified to offer decompressive surgery, provided imaging shows a likely responsible vascular conflict.

Time has come for working groups, with specialists in HT, to establish criteria for patients to be candidates: patients in whom HT has clinical peculiarities and even more pharmacological features, in favour of a neurogenic origin, namely, brainstem and/or IX–Xth nerve compression. Prospective studies should be launched with standardized protocols in patients with uncontrolled/unstable HT.

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Part II
Standards

Pineal Lesions: A Multidisciplinary Challenge

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Contents

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Abstract The pineal region is a complex anatomical compartment, harbouring the pineal gland surrounded by the quadrigeminal plate and the confluents of the internal cerebral veins to form the vein of Galen. The complexity of lesions in that region, however, goes far beyond the pineal parenchyma proper. Originating in the pineal gland, there are not only benign cysts but also numerous different tumour types. In addition, lesions such as tectal gliomas, tentorial meningiomas and choroid plexus papillomas arise from the surrounding structures, occupying that regions. Furthermore, the area has an affinity for metastatic lesions. Vascular lesions complete the spectrum mainly as small tectal arteriovenous malformations or cavernous haemangiomas.

Taken together, there is a wide spectrum of lesions, many unique to that region, which call for a multidisciplinary approach. The limited access and anatomical complexity have generated a spectrum of anatomical approaches and raised the interest for neuroendoscopic approaches. Equally complex is the spectrum of treatment modalities such as microsurgery as the main option but stereotactic radiosurgery as an alternative or adjuvant to surgery for selected cases, radiation as for germinoma (see below) and or combinatorial chemotherapy, which may need to precede any other ablative technique as constituents.

In this context, we review the current literature and our own series to obtain a snapshot sentiment of how to approach pineal lesions, how to interrelate alternative/competing concepts and review the recent technological advances.

Keywords Pineocytoma • Germ Cell Tumours • Pineal Cyst

Anatomy and Physiology

The pineal gland in adults is a neuroendocrine organ of nearly 1 cm diameter and attributed to the diencephalon. It is located underneath the splenium of the corpus callosum and rostrodorsal to the tectum bordering on to the third ventricle; the lateral borders are the cerebral peduncles and the thalami (Fig. 1).

Although the pineal gland has a relatively redundant arterial supply by the A. lamina tecti and the A. choroidea posterior for surgical purposes, it is more important to consider the anatomy of the venous structures in this region, since these drain the vitally essential structures of diencephalon and mesencephalon. Hence, a venous lesion possibly leads to congestion and severe damage of aforesaid cerebral areas.

The internal cerebral veins, draining blood from pallidum, striatum and dorsal thalamic parts, form together with the basal veins of Rosenthal the internal cerebral vein of Galen. The confluence is located on top of the pineal gland. The vein of Galen also contains drainages from the occipital and upper cerebellar regions and flows into the straight sinus.

Although the localisation and anatomical characteristics of the pineal body were well known to ancient scientists such as Galen and Hippocrates, its function and

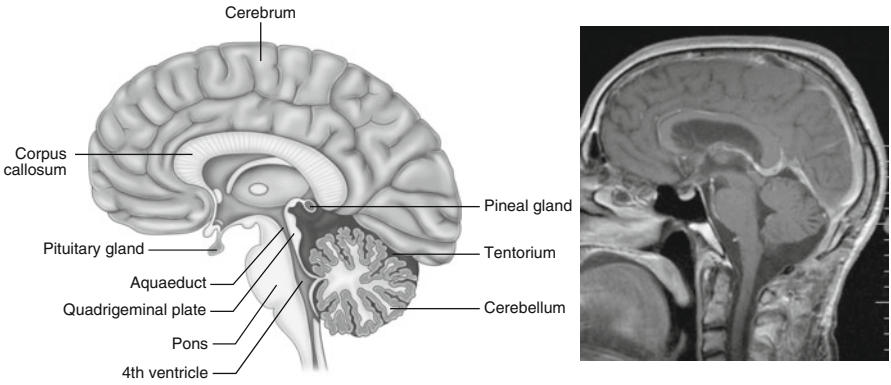

Fig. 1 Illustration of the median sagittal view of the brain (*left*). Same view in MRI, T1 + CM (*right*)

relevance as a gland started to be investigated in the eighteenth and nineteenth century under "modern" scientific points of view [14]. The detailed hormonal function, in particular the production and secretion of melatonin, was described even much later in the 1950s by Lerner et al.

To date, there are several different aspects of the pineal function discussed. As a photosensitive organ with light depending secretion activity this gland is supposed to have an influence on circadian and circannual functions of human body such as sleep-wake rhythm and the release of gonadotropic pituitary hormones, which regulate the pubertal maturation processes.

Some more effects, e.g. on dendritogenesis [18], renal function [34] and immune function [10] as well as antioxidant activity, were also described lately. Finally, melatonin is also used in therapy of mental disorders, especially depression and it is supposed to have a positive impact on cancer therapy.

Clinical Aspects

The most common symptoms leading to the diagnosis of a lesion in this site, such as hydrocephalus and signs of a related ICP as well as visual disorders [12, 35, 57], are well explained by the anatomical location, since a lesion in the pineal region may occlude the Sylvian aqueduct or affect tectal and other mesencephalic structures. The latter rarely leads to paresis or paraesthesia. Also, seizures are not common; they may rather be related to a decompensated hydrocephalus than to the tumour location.

Regarding the physiological functions of the pineal gland, one may also expect hormonal disorders (e.g. precocious puberty) or a malfunction of the circadian rhythm (insomnia) other.

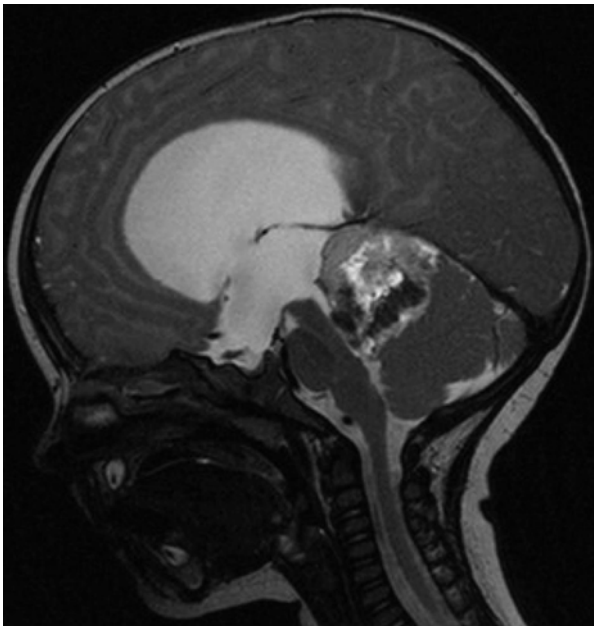

Fig. 2 Occlusive hydrocephalus caused by an ATRT of the pineal region in a 9-month-old male patient (MRI, T2, sagittal)

Hydrocephalus

Hydrocephalus itself is seen in the majority of the cases, often as the presenting sign. Konovalov describes in 58 % of cases a symptomatic hydrocephalus, Cho et al. [12] in about 60 % and Vaquero et al. [57] even in up to 100 % of their cases, which, however, were not all symptomatic. The acuity of the symptoms is mainly depending on the severity of the hydrocephalus and not on the tumour itself. Headaches are also frequently mentioned as a leading symptom in the literature, but there is no differentiation made between those related to raised ICP and/or hydrocephalus and non-specific headaches (Fig. 2).

Ophthalmological Symptoms

Visual disorders in general terms are reported to be one of the most common symptoms in patients with pineal region tumours [3, 12, 35, 57]; nevertheless, most authors do not differentiate between the diverse ophthalmological symptoms explicitly. Although Parinaud's syndrome (upward gaze palsy, accommodative paresis, convergence-retraction nystagmus) is a typical phenomenon observed in patients with lesions affecting the superior colliculi of tectum, we in fact observed in our series, that other complex and unspecific visual disorders are supposed to be at least just as common. Due to advances in surgical techniques visual or oculomotoric deficits, as a complication to surgical treatment (especially to open surgery), do not occur very often and once presenting, they are usually transient and totally reversible [6].

Circadian Rhythm

Not only the influence of the circadian rhythm on growth of malignancies [27] but also the interaction between cancer therapy and the sleep-wake pattern is subject of scientific interest time and again; fatigue is also a well-known phenomenon related to adjuvant therapy. But a disturbance of the circadian rhythm related to a pineal region tumour is not reported very often in the literature. Mandera et al. [39] describe "very high night levels of melatonin in patients with pineocytomas" but no details about its influence on sleep-wake modalities. Engel et al. [21] observed only in 1 out of 13 cases circadian rhythm disturbance which also occurred in a patient suffering from pineocytoma. Larger series even do not mention this subject [12, 35, 57]. Obviously this symptom is either occurring rarely in these cases or it also may be observed more often but mostly misunderstood as an unspecific side effect of the therapy or a paraneoplastic phenomenon of the neoplasia in general. In our series of 114 patients being operated on pineal region lesions, we observed only one person complaining from sleeping disorders initially, four more patients suffered from similar symptoms post-operatively. In all cases, the intake of melatonin (Circadin®) helped to relieve the complaints.

Endocrinology

Although the pineal body is a part of the neuroendocrine system, hormonal disorders occur only in few cases of patients with tumours in this area. In our series, there only were 2 patients out of 114 suffering from endocrinological symptoms.

Diabetes insipidus as a symptom in the context of a pineal region tumour was described more than 60 years ago [30]. Since then other symptoms, such as precocious puberty and panhypopituitarism, also were related to these lesions.

Some authors even postulate a correlation between entity (namely germ cell tumours) and the specific endocrinological deficiency: Vaquero et al. [57] report on precocious puberty (3 germinomas and 1 embryonal carcinoma), diabetes insipidus (4 germinomas and 1 glioblastoma) and panhypopituitarism (one germonima). The lack of large multicentric observations makes it difficult to draw reliable conclusions of these observations. Nevertheless in most of these cases, the initial symptoms disappear when the underlying disease is treated successfully.

Some germ cell tumours (GCT) characteristically secrete proteins or hormones, which can be detected in CSF and serum. The value of the laboratory results is subject to discussion (section "Serum and CSF markers") where some typical patterns or tumour marker constellations can be defined related to specific tumours (Table 1).

Epidemiology

Tumours of the pineal region are rare lesions of different entities amounting about 1 % of intracranial tumours. The incidence of the subgroups varies regionally; tumours of germ cell origin—as a major subgroup—occur much more often in the

Table 1 Possible tumour marker constellations in serum or CSF as described by Janss and Mapstone [32]

Tumour type	α-Fetoprotein (aFP)	Chorionic gonadotropin (ßHCG)	Placental alkaline phosphatase (PLAP)
Germinoma	–	±	+
Teratoma	–	–	±
Malignant teratoma	±	±	±
Undifferentiated germ cell tumour	±	±	±
Choriocarcinoma	–	+	±
Endodermal sinus tumour	+	–	±
Embryonal cell tumour	+	+	±
Pineocytoma	–	–	–
Pineoblastoma (PNET)	–	–	–

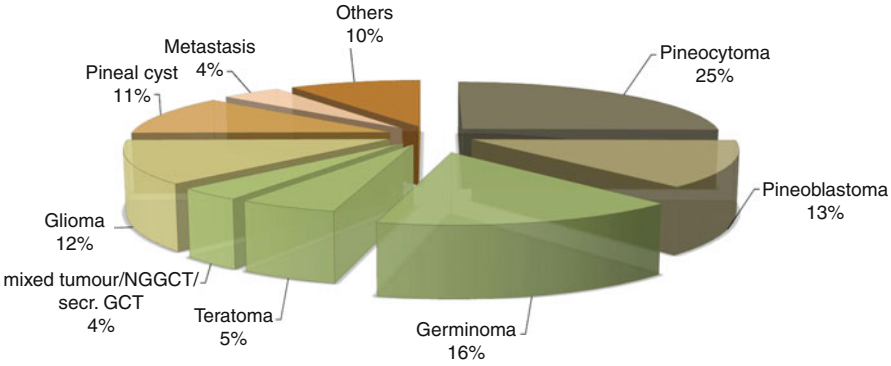

Fig. 3 Distribution of the diagnoses in our series ($n = 114$)

Far East, especially in Japan than in Northern Europe or the United States (see also section "Germ cell tumours"). Other entities have a more evenly distributed incidence irrespective of the geographic conditions.

GCT and pineal parenchymal tumours (PPT) make up the major part of the entities, and male patients dominate in the cohorts as well as children and young adolescents. We counted in our series 114 patients with a mean age of 26 years operated on lesion of the pineal region, from which 57 % were of male gender. The histological distribution of the operated lesions is shown in Fig. 3.

Neuro-oncological Aspects

Pineal region tumours (PRT) include multiple entities of different biological characteristics; therefore, the subgroups should be considered and evaluated separately in order to define more specific diagnostic and therapeutic pathways.

According to the origin of the tumour, the WHO classification of tumours of the central nervous system currently distinguishes between following entities:

- Germ cell tumours (GCT)
  - Germinoma
  - Embryonal carcinoma
  - Yolk-sac tumour
  - Choriocarcinoma
  - Teratoma
    - Mature
    - Immature
    - Teratoma with malignant transformation
  - Mixed germ cell tumours
- Tumours of the pineal parenchyma (PPT)
  - Pineocytoma
  - Pineal parenchymal tumour of intermediate differentiation
  - Pineoblastoma
  - Papillary tumour of the pineal region
- Tumours of supportive and adjacent structures
  - Astrocytoma
  - Meningioma
- Non-neoplastic tumour-like conditions
  - Pineal cysts
  - Vascular malformations
- Metastases

This classification is mainly histologically oriented. Taking clinical features of the GCT into account, some authors also group embryonal carcinomas, yolk-sac tumours (synonymous with endodermal sinus tumours), choriocarcinomas and immature teratomas as non-germinomatous germ cell tumours (NGGCT, [29]), which are treated in a similar way. Alternatively, some authors prefer to differentiate between secreting and non-secreting germ cell tumours. This definition is closer to the actual clinical approach (see also chapter "Minor and repetitive head injury").

Diagnostics

Imaging

The progressive calcification of the pineal gland during life makes it visible in the CT scan at least in adults. Other details of any pathological lesion in this area are only insufficiently shown by this imaging modality. MRI without and with contrast is the modern and adequate method to perform a useful and informative preoperative imaging. It is of utmost relevance to have all three planes imaged and preferably

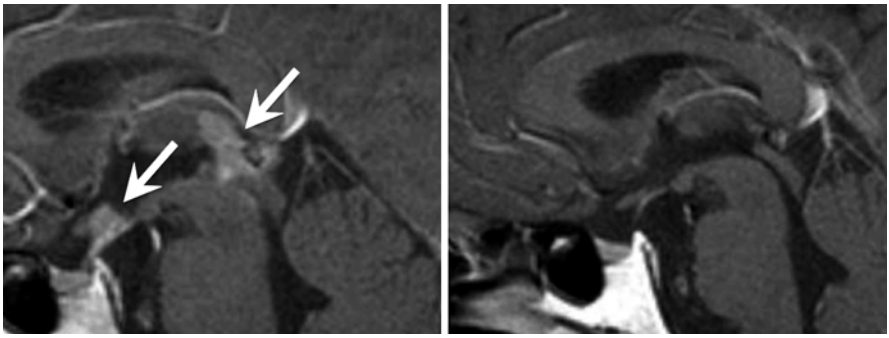

Fig. 4 Multilocular intracranial germinoma in a 21-year-old male before (*left*) and after (*right*) radiotherapy. The *arrows* show lesions in the perisellar and pineal region (MRI pictures courtesy of PD Dr. J. Flitsch)

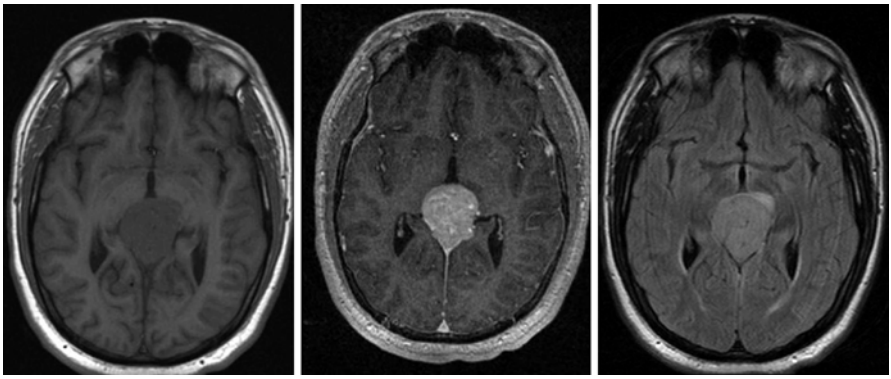

Fig. 5 A 16-year-old boy with a monolocular pineal region germinoma (*from left*: MRI T1, T1 + CM, TIRM)

even a sequence in which CSF flow can be assessed (see below) [44]. Parker and Waziri even consider a pre-operative full craniospinal MRI as necessary, since spinal CSF metastases occur sometimes in cases of pineal tumours, specially the malignancies and germ cell tumours. Multilocular lesions around the midline are suspected to be germinomas (Fig. 4). For some tumour entities, the demonstration of craniospinal or intracranial dissemination of the tumour is relevant for tumour staging and the allocation to stage specific adjuvant treatment protocols and selection of therapy regimens (Fig. 5).

Extensive imaging is relevant as it allows for the visualisation of the exact anatomical conditions around the tumour for surgical planning (tentorial angle, position of the quadrigeminal plate) and may reveal areas or infiltration, attachments and the vascular situation.

Specific vascular imaging by angiography is normally unnecessary, as arterial structures do not play an important role in surgical procedures or planning for

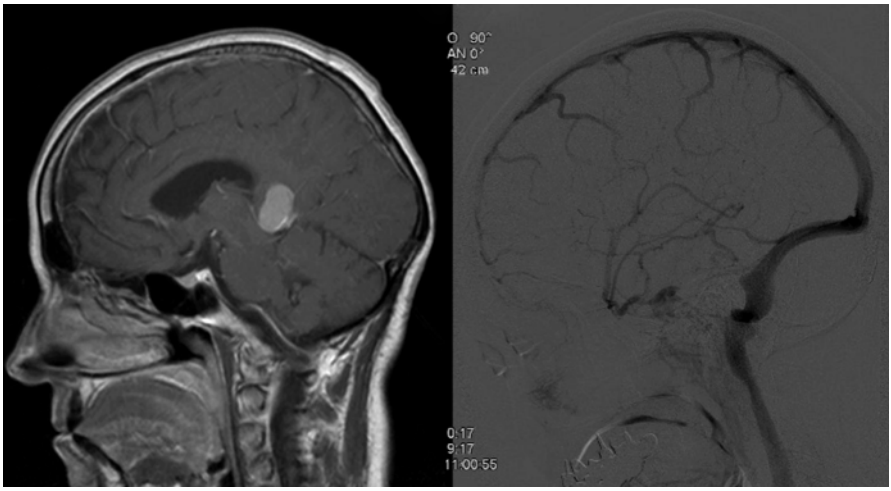

Fig. 6 MRI, sagittal, T1 + CM (*left*) of a 60-year-old woman with a pineal region meningioma compressing the inner cerebral veins from above, leading to anterograde flow in the internal veins as an expression of long-standing collateralisation as seen in the DSA (*right*). The vein of Galen does not seem to have any drainage into the straight sinus, allowing for dissection of the tentorial origin of the tumour. Because of the downward venous displacement, a midline parieto-occipital partially transtentorial approach is chosen here

parenchymal lesions of the pineal region. Vascular lesions like small AVMs (not part of this series) are of course different. An exception is lesions possibly involving the venous system at the tentorial notch where haemodynamics and collateralisation and position of the veins determine the approach and the options to transect venous structures (Fig. 6).

Whatever modern MR imaging provides as information about the anatomical and local conditions prior to planning any procedure, none of the imaging modalities are currently able to substitute for histological evaluation and except for secreting or multilocular tumours with cerebrospinal fluid cytology no diagnosis can be made based on images alone (Fig. 7) [20].

CSF Flow Measurements

Modern MRI techniques, e.g. special T2 sequences, can illustrate CSF flow through turbulences caused by the flow void resulting from fluid turbulences (Fig. 8). This indeed can be helpful in order either to monitor the patency of the aqueduct in case of suspected obstruction or to check the functional efficiency of surgically made alternative CSF pathways (so-called endoscopic ventriculostomy, see also section "Endoscopic methods").

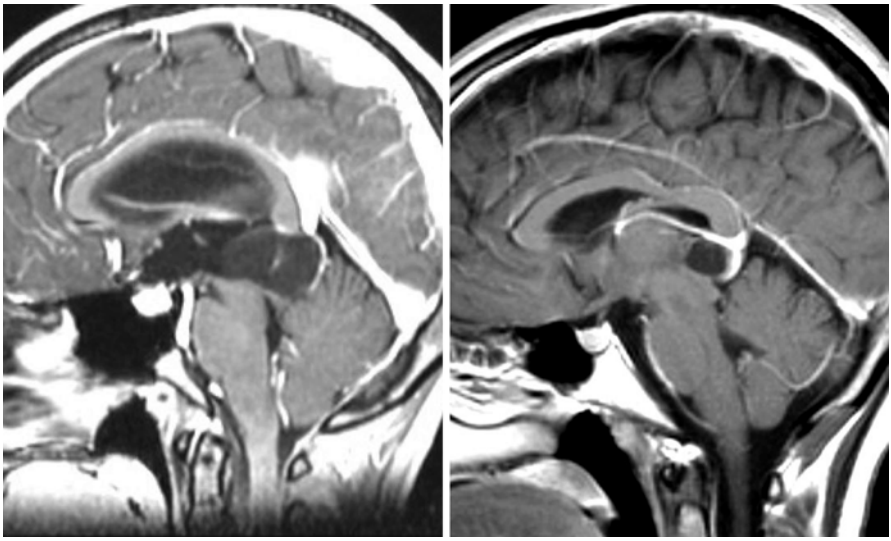

Fig. 7 MRI sagittal, T1 + CM of a 28-year-old woman with a pineal cyst (*left*) and T1 + CM of a 27-year-old woman with a pineocytoma (*right*). Radiologically one cannot distinguish reliably between one and the other. Both lesions present a cystic structure with minimal contrast medium enhancement in the margin area

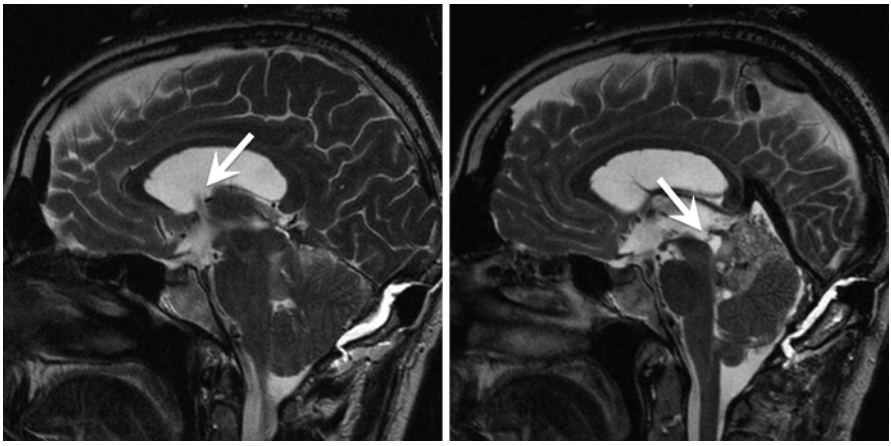

Fig. 8 MRI, sagittal T2. There is a flow void signal seen in the foramen of Monro (*left arrow*), while the entrance to the obstructed Sylvian aqueduct is dilated and lacking a flow void (*right arrow*)

Serum and CSF Markers

Mainly GCT and some of the NGGCT are supposed to produce markers, which can be detected in serum and/or CSF. Negative markers do not exclude the presence of GCT, especially determination in serum is not reliable. CSF markers have a more

reliable diagnostic yield, but a lumbar puncture is critical in the majority of the cases due to the related occlusive hydrocephalus of the lesions in this area. As some of the pineal patients present with acute CSF pathway obstruction, it is mandatory to send CSF for marker analysis when performing either external ventricular drainage or a third ventriculostomy [9].

Treatment Methods

Open Surgery

Despite of the rise of minimal invasive methods, open surgery remains the favoured surgical procedure in most of the cases; especially benign lesions should be removed totally in first line. The microsurgical technique is the established common practice [6, 12, 19, 35]. Thanks to the advances in surgical techniques as well as the perioperative management the number of complications nowadays is acceptably low (Bruce and Ogden [6], see also section "Monitoring: neuronavigation")—at least as long as the operations are performed in experienced centres. One of the main advantages of the open surgery is the possibility to remove the tumour totally, which is the main therapeutic goal in benign tumours. In all other cases, it provides the possibility to obtain a representative specimen in order to come to a reliable histological diagnosis and to reduce the tumour volume as an optimised pre-condition for a more effective adjuvant therapy [5]. Especially in the context of frequently mixed tumours (germinoma and teratoma), one may understand the importance of definitive specimens.

A positive side effect of tumour removal is the elimination of aqueductal compression and subsequent hydrocephalus, which allows for a long-term therapy without using a shunt.

As far as surgical approaches are concerned, there are many different ways to reach the pineal region. The supracerebellar infratentorial and the occipital transtentorial approaches are mentioned to be the most common ones; each method provides its advantages or disadvantages, which will be discussed below; the final choice, which approach to chose, depends on the specific anatomical conditions of the patient, the location and extent of the tumour as well as the personal experience and the preference of the surgeon performing the procedure.

Approaches

Supracerebellar Infratentorial

This approach, first described by Fedor Krause (1856–1937) in the 1920s, was optimised in the 1970s by the upcoming microsurgical techniques [53, 54]. It often is performed on the patient in semi-sitting position. Prone positioning can be chosen alternatively. This approach is strictly extracerebral and extracerebellar with no need to incise brain tissue.

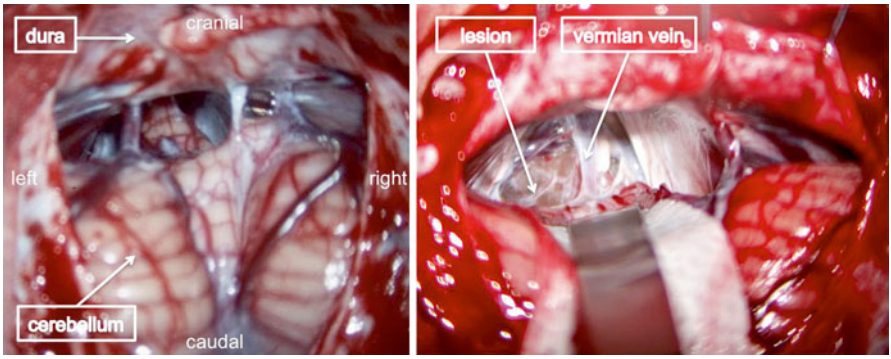

Fig. 9 Microscopic view of the infratentorial supracerebellar approach. In this case, the individually highly variable posterior cerebellar veins draining into the tentorium (*left*) were cut to depress the cerebellum and move the vermis sideways, leaving the rostral veins hidden in the arachnoid "curtain" behind the lesion (*right*) intact

Via a midline incision and a suboccipital craniotomy the dura is opened, so one may look infratentorially and above the cerebellum through the gained space into the pineal region. A thoughtful and unilateral sacrifice of cerbellar veins remains without any consequences as long as care is taken of the precentral vermian vein, which may lead upon its occlusion to cerebellar infarction (N de Tribolet, personal communication, 2011 see also Fig. 9). This approach enables the surgeon especially to have a good overview over the venous structures in this area. The cerebellum is depressed caudally due to the gravity while patient is positioned half-sitting; using a retractor can support this effect. Through this approach to the pineal region is reachable without incising brain tissue. Most authors prefer the sitting position; some also chose the prone position for this approach.

Occipital Transtentorial

As an alternative a parasagittal craniotomy can be performed in the occipital region over the non-dominant hemisphere and by approaching the tentorium via a parafalcine interhemispheric route, it can be incised close to the midline. By this approach, the pineal region is reached from the dorsal upper part and consideration needs to be taken of the important venous structures of this area.

Parietal Interhemispheric/Transcallosal

Through this approach, which includes a craniotomy placed rostral to the aforementioned route, the pineal region can be reached via the midline interhemispheric space (also along the falx) and by dividing the dorsal part of the corpus callosum. Bridging veins may also appear as another obstacle. Accordingly this way is the

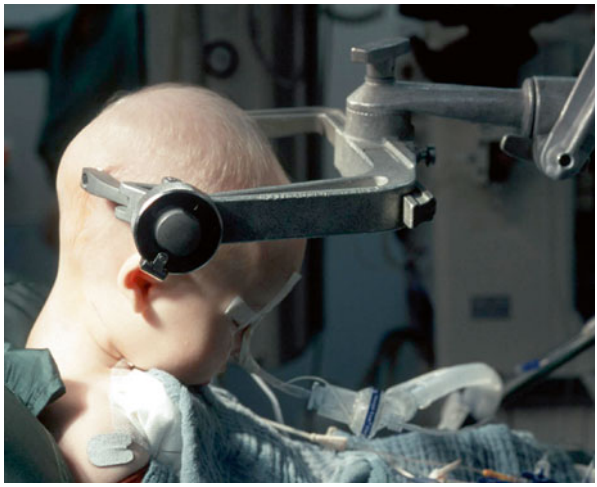

Fig. 10 Semi-sitting position of the patient with his head fixed in a Mayfield clamp

most traumatic one among the three described approaches. Nevertheless, it may be the appropriate choice as far as lesions in the dorsal part of the third ventricle adjoining the pineal region are concerned.

Positioning

Depending on the chosen approach, the location and extent of the tumour, there are several possible ways to position the patient. The sitting/semi-sitting position, which is mentioned to be the most common one, provides better and gravity supported depression of the cerebellum [53], especially when choosing the infratentorial supracerebellar approach.

The major risk of the sitting position is that of air embolism which is all the more dangerous in the presence of a patent foramen ovale (PFO). Without PFO, a massive air embolism can lead to pulmonary problems, but with PFO paradoxical air embolism can occur anywhere including the brain. To prevent or at least anticipate these complications it is recommended to perform a cardiac sonography prior to the operation in order to recognise the existence a PFO. Positioning of the patients with legs up, head maximally anteflected and body reclined as much as possible is crucial (Fig. 10). As air enters mostly trough venous bone channels, diamond drills to finish the craniotomy and bone wax are mandatory. After dural opening, air rarely enters the circulation. Nevertheless, constant intraoperative monitoring of the right atrium by Doppler or better echocardiography is mandatory. The involvement of dedicated neuroanaesthesia is part of the interdisciplinary approach to the pineal region.

As most patients have hydrocephalus and a dilated third ventricle, which is widely opened during surgery, symptomatic pneumocephalus is a not infrequent (Fig. 11) phenomenon. It remains a case-to-case decision whether to place an external ventricular drainage at the end of the procedure because in most cases the situation will resolve within the first-day post-surgery.

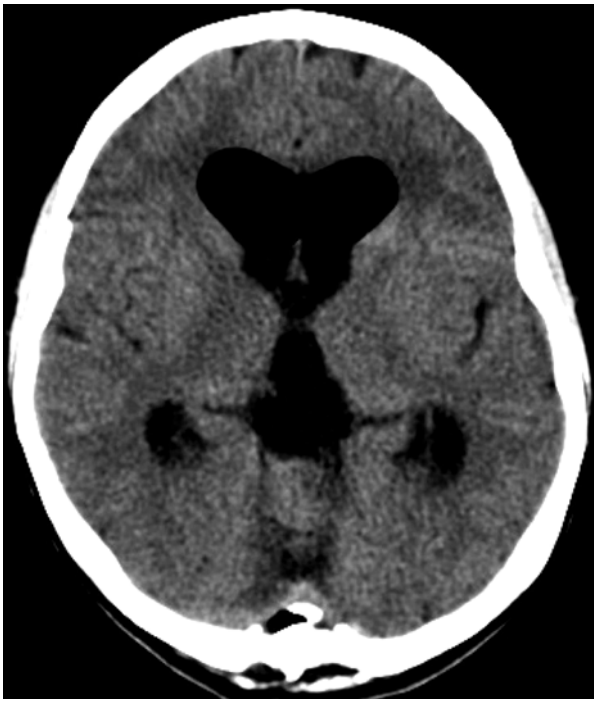

Fig. 11 Post-operative CT scan of a 27-year-old female patient with a pineal cyst. The initial post-operative symptoms (nausea, vomiting and headache) vanished completely after 4 days. She only was treated symptomatically with antiemetics and analgetics

Subdural hygroma or subdural haematoma (due to cortical collapse and excessive loss of CFS) may also theoretically ensue from the sitting position, but this was not observed in this series.

For the supracerebellar infratentorial approach, instead of a sitting or semi-sitting position, some authors suggest for all approaches the prone or Concorde positioning. This may be warranted in cases with severe PFO, but it has to be acknowledged that this has to be counterweighed against the necessity to retract cerebellum and a much more narrow surgical field.

Despite of the factual characteristics of each method, the choice for any of them remains not only a matter of personal experience but also preference of the surgeon.

Stereotactic Biopsy

Especially in critical cases with high (peri-)operative risk, like older patients with a very high likelihood of metastatic disease, a minimal invasive and reliable biopsy method may be needed to confirm a diagnosis. Stereotactic procedures are used in neuro-oncological cases for several decades and are well established. The accuracy of this method concerning biopsies in the pineal region may depend on the expertise and experience of the surgeon, although some authors postulate the same accuracy irrespective of the performing centre and the localisation of the biopsied lesion [48].

The published diagnostic accuracy ranges from 83 % [35] to 94 % [48], respectively 97 % [36]. Thus, the reliability is somewhat inferior to open surgery. The discussion about the superiority of the methods is ongoing but especially for a region in which very heterogeneous tumours are present, the necessity of a correct histological finding to determine adequate treatment pathways is well understood. From this series, it is felt that stereotactic surgery should only be contemplated in those cases with pineal lesions, in which open surgery may be contraindicated for whatever reason such as age-related general health, anatomy or purely confirmatory indication.

Endoscopic Methods

The opportunity not only to alleviate the occlusive hydrocephalus by endoscopic third ventriculostomy (ETV) but also to obtain CSF (in order to find pathological cells, markers, etc.) and even to do a biopsy of the tumour itself makes endoscopic methods part of the therapeutic armamentarium in the treatment of pineal region tumours.

Via a right frontal burr hole, the right lateral ventricle and the third ventricle can be visualised with an endoscope. The floor of the third ventricle is perforated and the incision dilated (ETV). By tilting the view backwards, while, e.g. using a flexible endoscope, the process can be reached for a biopsy.

The management of acute hydrocephalus is the symptom most influenced by ETV. Nowadays, in case of emergency, caused by acutely raised ICP due to an occlusive hydrocephalus, this minimal invasive method should be standard, not only to treat the acute symptoms and achieve a diagnosis with a low risk of complications but also to eliminate the sequelae of shunting, which as an emergency procedure is obsolete, or the management complications of external ventricular drainage [40]. Most authors report on series without any mortality or severe procedural morbidity [2, 59]. The additional benefit of an ETV is that in the majority of cases, which need to be operated, the collapse of the ventricular system is much slower which allows for generous space during surgery (personal observation).

Despite of the low risks and number of complications of endoscopy, the diagnostic yield remains suboptimal, possibly because an ependymal coverage or the dilated posterior commissure are biopsied. The error rates amount up to 25 % [2]; after all other authors report on 6 % [46] and 11 % [59], respectively. Therefore, stereotactic biopsy is more effective in case a biopsy is needed [8].

Monitoring, Neuronavigation

Depending on whether mesencephalon and/or brainstem structures are involved, modern monitoring techniques such as electrophysiological investigations should also implemented into the surgical procedural setting. The well-defined position of the pineal region and the non-variable anatomical conditions of the approach to this

Table 2 Perioperative complications in 115 procedures (114 patients)

Complications	*n*	*%*
Haemorrhage	6	5.2
Infection	3	2.6
CSF leak	5	4.3
Air embolism	2	1.7
Myelopathy	1	0.9
Total	*17*	*14.8*

area preclude any use of navigational tools as they would most likely be completely misleading and cannot compensate for the proper recognition of the defined regional anatomy.

Complications

Irrespective of the technique, haemorrhage and infection are described to be the main surgical complications. Nevertheless, they rarely are severe; major neurological morbidity or even mortality remains exceptional [6, 35]. In our series, we counted complications in 16 out of 114 cases (115 procedures!). In only two of them we observed relevant neurological deficits; one due to a haemorrhage which underwent a decompression, the other caused by the positioning of the head (myelopathy), which made a laminoplasty of the cervical spine via necessary. The CSF leak only needed to be revised in one case. Air embolism was only registered intraoperatively in two cases, but both remained clinically mute. None of the patients suffered from any major neurological or other deficits caused by the procedures by discharge (Table 2).

Visual deficits as well as hydrocephalus due to surgery are rarely found; patients do usually not report endocrine surgical complications or disturbance of the circadian rhythm but when specifically questioned, they may admit changes in their sleep/wake cycle. Since regularly interviewing the patients, we had four patients with such disturbance, which was completely controlled with melatonin medication (Circardin®).

CSF leakage was observed in four cases in our series, which only led in two cases to a surgical revision.

The sitting position carries the risk of air embolism, which can be minimised by appropriate measures as mentioned above. Accordingly, none of the larger series report on such a complication. In our series, we also had no air embolism, which became clinically apparent with post-operative symptoms. Despite the best management, it nevertheless cannot be excluded and we saw two cases of which one became clinically relevant during surgery by pulmonary problems. Repositioning of the patient by tilting the table backwards and raising venous pressure was the only option and the case could still be finished in an orderly fashion and the post-operative course was unremarkable

Pneumocephaly, due to this positioning method, however is seen regularly. It may specially cause nausea, headache and delayed recovery in the first-week post-surgery.

These symptoms, however, often improve during the first 3–5 post-operative days even without external ventricular drain and no general rule can be applied as to who should get a drain and who not. Early in the series, a ventricular catheter was inserted into the supracerebellar region through the posterior approach, but these were cases which had subsequent CSF leaks after drain removal, so that this policy has been abandoned for placement of a right lateral ventricular drainage when felt necessary.

Among the minimal invasive methods, stereotactic biopsy offers a better diagnostic yield comparing to the endoscopic biopsy, while the latter bears a substantially lower complication rate. Accounting to the necessity of a reliable histological finding, open surgery, performed in experienced centres by experienced surgeons, may be the superior method to both achieve a reliable diagnosis and run an acceptable risk of perioperative complications.

Therapy of Occlusive Hydrocephalus

The occlusive hydrocephalus is the most common symptom in patients with pineal region tumours. This may also lead to raised ICP and related acute symptoms. Total tumour resection is more and more considered to be the ideal way to restore the natural CSF drainage, while permanent shunting was performed routinely or at least very often in the past (Vaquero et al. [57]: 66 %, Konovalov and Pitskhelauri [35] 54 % of the cases). In cases presenting with acute symptoms caused by raised ICP the choice, which CSF drainage method to perform, should depend on the overall strategy and anticipated histology. If resection is the goal, it should be done with minimal delay so that no extra procedure is necessary. No shunt should be placed by centres before referring the patient. If hydrocephalus needs to be treated, ETV is preferable to external drainage [35], especially because the ventricles will collapse slower and the advantage of a wide third ventricle for drainage is maintained. If germinoma is suspected, external drainage may be acceptable as it allows for access to CSF for cytology. Endoscopic or stereotactic biopsy may firmly establish the diagnosis and with therapy, the CSF obstruction will resolve rapidly. Patients, who do not respond to an ETV permanently or sufficiently because they also have a malresorptive component, can be treated by permanent shunting. Seeding along the shunt—especially in cases with malignancies—is a rare complication, which should be contemplated critically [31, 41, 45].

Diagnosis-Related Therapy Regimens

Pineal Parenchymal Tumours (PPT)

Tumours arising from pineal tissue itself are, as well as germ cell tumours, lesions that occur most frequently in the pineal region (Schild et al. [50]: 30 %, Tate et al. [55]: 35 %). These include according to the actual WHO classification:

- Pineocytoma WHO I
- PPT of mixed or intermediate differentiation WHO I/II
- Pineoblastoma WHO IV

Pineocytomas amount to 45 % of the PRT, occurring in young adults but without gender predilection [23]. Adjuvant methods seemingly do not improve tumour control or survival in cases suffering from these slow growing benign tumours. Aggressive surgical treatment (total or gross total resection) in fact influences both factors in a positive way; therefore, open surgery is established as standard therapy regimen for these patients. In those rare cases with spinal dissemination craniospinal adjuvant, radiotherapy or even chemotherapy should be considered as well [16, 23].

PPT of mixed or intermediate differentiation presents in a similar gender distribution but concern older patients with a mean age about 30 years [23]. Therapy options for these tumours remain controversial. An accurate histological diagnosis is the main issue to determine how to proceed. Accordingly minimal invasive biopsy bears the risk of an inappropriate tissue sample, which can mislead to a false diagnosis. Open surgery may be the superior method to gain a reliable tissue sample [23]. In case of open surgery, at least tumour debulking should be performed, since smaller tumour volumes may provide more effective adjuvant therapy.

Pineoblastomas also amount to 45 % of the PPT. Patients suffering from this tumour are the youngest in this subgroup (mean: 13–18 years, [23, 50]). These aggressive tumours, considered as supratentorial primitive neuroectodermal tumours (PNETs), are more often associated with spinal dissemination, which makes a CSF examination and craniospinal imaging necessary. According to the histological character of these tumours, the treatment also is similar to that of PNETs, which includes surgery, craniospinal radiotherapy and chemotherapy. The extent of the surgical resection is an important prognostic factor [11, 26, 55] as well as the age of the patients; the younger they are, the higher is the mortality rate [17]. Pineoblastomas may rarely be associated to congenital bilateral retinoblastomas; in this context, one may find the expression “trilateral retinoblastoma” as a description to this condition.

A quite rare entity is the *primary papillary tumour of the pineal region* (PTPR). It first has been described as a new distinct entity by Jouvet et al. [33]. Since then there are mainly case reports published on this subject, reporting on a lesion, which histologically is difficult to be diagnosed [8]. Not only the histological issues but also the biological behaviour of the tumour and the clinical course of these patients make the WHO classification as a grade II to III tumour understandable: Rapid tumour progression and recurrences are often seen in these cases as published in some case reports [49] as well as in the largest retrospective series to date [24].

According to the biological character of the tumour and the experience based on the natural history of the presented cases, total surgical resection is suggested to be the ideal therapy followed by radiotherapy, although an evidence-based standard therapy regimen is still to be developed. The latter indeed is not easy regarding the low number of described cases and the actuality of this new entity definition.

Germ Cell Tumours

GCT is another common entity in this site, which accounts for 31 % of pineal lesions in Europe (Russia/USSR, [35]), 68 % in the USA (SEER Database, [1]) or even more than 80 % in Asia [42]. They mainly occur in children and young adults of male gender and are located in the midline.

Depending on their origin, a distinction is made between germinomatous and non-germinomatous GCT (NGGCT, see also chapter "Is there a place for microsurgical vascular decompression of the brainstem for apparent essential blood hypertension? A review"). The latter arise from differentiated or undifferentiated embryonal tissue, while germinomas originate from primordial germ cells. All of these tumours, despite of mature teratoma, are classified as malignant, germinomas though are clinically less aggressive. In order to plan therapeutic strategies, it is important to be conscious of the fact, that about ¼ of the germ cell tumours in the pineal region are from mixed origin, i.e. containing two or more histological subtypes [51]. This again highlights the importance of biopsy accuracy and preferably large specimens for accurate evaluation.

From the clinical point of view, GCT are divided into three therapeutic subgroups:

Best treatment method for *mature and pure teratomas* is total surgical resection. These benign tumours arising from differentiated embryonal cell groups grow slowly, and they accordingly do not respond to chemotherapy or irradiation. Teratomas do not secrete tumour markers, so neither CSF nor serum examination could give any hints concerning a diagnosis.

Pure germinomas are well known as radiosensitive lesions; even full remission can be achieved by radiotherapy. Multilocular presentation around midline structures (e.g. perisellar or close to the third ventricle) and spinal dissemination are typical diagnostic and clinical features. Therefore, surgical resection in these cases is more and more doubted to be a reasonable method [25, 35, 43]. Furthermore, they rarely secrete tumour marker proteins, i.e. hPLAP and ß-HCG. Though negative markers do not exclude the presence of a germinoma, but positive markers both in serum and CSF as well as multifocal finding are highly indicative for it [13].

The remaining entities among this group, summed up as *NGGCT*, are considered to be more aggressive lesions, and they are more likely to produce tumour markers. Also, in these cases, surgery is not supposed to be the first-line therapy rather than embedded in a multimodal therapeutic strategy consisting of neoadjuvant chemotherapy, surgical resection of the remaining tissue and finally radiotherapy, which may include not only the target area but the whole craniospinal axis [9, 29].

Since GCT amount to the major part of the pineal region tumours and they often are of mixed cell origin, following therapy strategy is taken into account: In case of positive radiological signs and positive markers predicting a germinoma, irradiation is the first-line treatment option. If the diagnostic findings rather indicate non-germinoma GCT, the therapy is started by neoadjuvant chemotherapy. Remaining

tissue after first-line therapy is always subject to surgical resection in the concept of a "second look" which is even prescribed in many of the paediatric oncological treatment protocols; post-operative radiotherapy is obligatory in case of NGGCT.

In case of non-secreting tumours histological diagnosis is indispensable.

Pineal Cysts

Therapy regimens for these benign lesions remain controversial. They count among non-neoplastic tumour-like conditions as defined by WHO; autopsy series reveal prevalence rates between 25 and 40 %, which correlates to the radiographic results of healthy adult series examined by MRI [15, 47]. Only a small part of these cysts become symptomatic. Their percentage among operated pineal region lesions range between 1 % [57] to 8.9 % [35] or 10.8 % [47]. Based on these statistics, some authors advocate therapy to be limited to symptomatic cases, especially regarding the fact that they rarely tend to grow or cause relevant symptoms.

Even therapy methods are subject to discussion. Surgeons familiar to minimally invasive and endoscopic methods favour this approach, which sometimes only allows a fenestration and biopsy of these lesions [52]. Open surgery is considered to be the "established" way to complete resection. Advocates for open surgery often point out that cystic pineocytomas can radiologically be mistaken for pineal cysts, which actually is doubted by some authors (Fig. 12) [22].

Gliomas

Gliomas in this region usually arise from the tectum. They occur mainly in the paediatric age group and are described to be as common as pineal or germ cell lesions in this area [7, 35]. Being intrinsic and by nature infiltrative to a mostly functional quadrigeminal plate, they are usually not amenable to gross total resection. Their therapy follows the principles of therapy regimens for gliomas with decompression/biopsy to obtain reliable diagnosis and grading and then depending on grade chemotherapy, radiation or both [4]. Low-grade lesions may be just observed until regular follow up by MRI will reveal progression [57].

Metastases and Other Lesions

Meningiomas of the pineal region originate from the anterior borders of the tentorium or even the confluence of the inferior sagittal sinus and the vein of Galen. They have no specific biology, but they deserve special surgical consideration as they have an intrinsic relationship with the veins in that region and that is why these tumours when anticipated are the only ones where conventional digital subtraction angiography (DSA) may be indicated (Fig. 6). Some authors suggest non-invasive diagnostic methods such as 3D-computed tomography angiography as a reliable

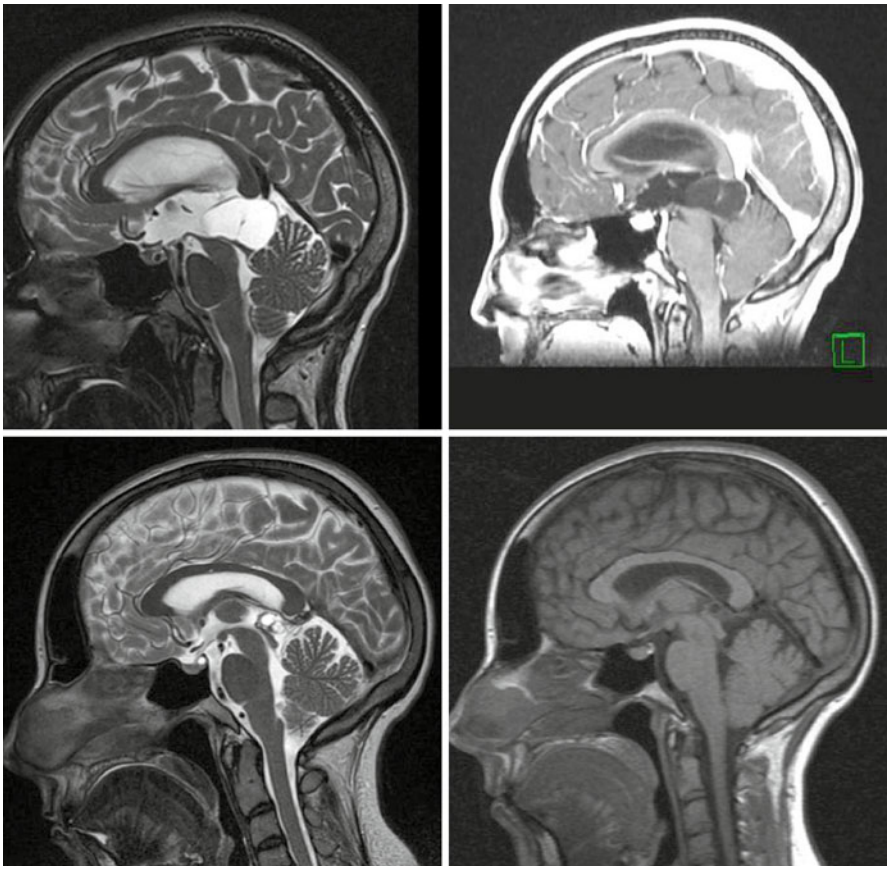

Fig. 12 Different manifestations of a pineal cyst. MRI, sagittal, T2 (*left*), T1 (*right*)

tool for planning operative procedures [37]. Because of their relationship with the venous system, which is either obliterated, encased or downwardly displaced, the surgical approach may vary from the pure infratentorial supracerebellar approach but might be modified to a midline, occipital transtentorial approach.

Metastases are seen in this region very rarely. They often are not mentioned as a distinct entity in the larger series [7, 35]. Nevertheless, the therapeutic strategy including operative options has to be in accordance with the treatment modalities of primary tumour entity.

Radiosurgery

Because of the often well-defined and deep-seated location, patients who are seen in centres with limited experience with microsurgery in this region are often referred to radiosurgery as initial treatment. Reviewing the literature, there are only few evaluated experiences with this technique in treatment of pineal region tumours;

confirming a diagnosis however remains mandatory before initiating radiosurgery [28], which is reserved for locally confined tumours, i.e. pineocytomas and metastases. Also, for incompletely resected tumours, radiosurgery to the tumour remnants has been advocated [58]. With slow growing lesions, follow-up times are too short so that frequently "stable disease" is a common outcome. The technique has been shown to be feasible [60] (as to be expected from radiosurgery) and is likely as efficacious as external beam fractionated radiotherapy which in the case of malignant lesions is to be preferred as it needs to be applied to larger volumes, often even craniospinal.

Interstitial radiotherapy with I-125 implants is not widely performed and there are only few reports which describe feasibility and efficacy in a limited series of cases [38], but in experienced hands it may be a technique which can complement the treatment options if all else has been evaluated.

Outlook

Successful treatment of pineal region tumours requires long-term experience with the variety of lesions and the biological and clinical aspects of each tumour entity. Large multicenter series do not exist and advances will only come from centres, which because of a broad referral base will accumulate sizeable institutional series with homogeneous treatment modalities. The complex nature of these lesions requires close cooperation between neuroradiology, neuropathology, paediatrics and (radiation)-oncologists. The broad spectrum of diseases in this region calls for specialisation and interdisciplinary consultations to achieve adequate and optimal outcome for these technically challenging cases.

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Cavernous Sinus Meningiomas: Imaging and Surgical Strategy

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Abstract Cavernous sinus (CS) meningiomas which are by definition those meningiomas which originate from the parasellar region are difficult skull base tumors to deal with. For deciding the most appropriate surgical strategy, surgeons need detailed preoperative neuroimaging. The vicinity of the tumor with the vital and highly functional neurovascular structures, tumor extensions into the basal cisterns and skull base structures, and the arterial vascularization and venous drainage pathways, as they shape operative strategy, are important preoperative data to take into account. Thin section CT scan with bone windows, 3D spiral CT reconstruction, MRI, MR angiography, and DSA performed with selective arteriography including late venous phases give those required detailed informations about the tumor and its relation with neurovascular and bony structures. The type of craniotomy and complementary osteotomy and the usefulness of an extradural anterior clinoidectomy with unroofing the optic canal can be decided from preoperative neuroimaging. Data collected also help in determining whether extensive exposure of the middle cranial fossa is necessary to ensure substantial devascularization of the tumor and whether proximal control of the internal carotid artery (ICA) at its intrapetrosal portion might be useful. Study of the capacity of blood supply of the Willis circle is wise for deciding the need and way of performing an extra–intracranial bypass together with tumor removal. Currently the concept of operating only the tumors with extracavernous extensions and to limit resection to only their extracavernous portions is the most accepted way of treating these tumors. It was that strategy that was adopted in the senior author's 220-patient series.

Radiosurgery or stereotactic fractionated radiotherapy may complement surgery or can be only reserved for growing remnants.

Keywords Cavernous sinus • Central skull base • Meningioma • Neuroimaging • Parasellar lodge • Presurgical planning • Surgical removal

Abbreviations

CS	Cavernous sinus
CT	Computed tomography
DSA	Digital subtraction angiography
ICA	Internal carotid artery
MRI	Magnetic resonance imaging

Introduction

The meningiomas which originate from or invade the parasellar region commonly named "cavernous sinus" (CS) have two peculiarities that make them considered as particular entities. First, they are located deep at the cranial base, near the visual pathways, the hypothalamo–hypophyseal axis, the arteries of the Willis circle and

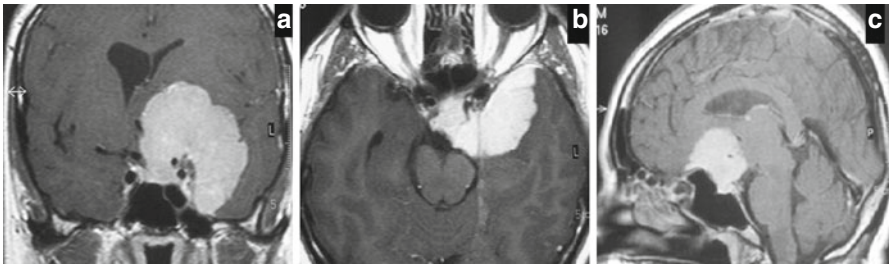

Fig. 1 T1-weighted MRIs with gadolinium showing central skull base meningioma with supero- and latero-sellar extensions and their relationships with the surrounding structures in coronal (**a**), axial (**b**), and sagittal (**c**) sections

their perforators, the motor ocular nerves, and the trigeminal system. Second, they frequently spread to the adjacent regions, namely, the supra- and latero-sellar space, pituitary region, orbital apex, sphenoid ridge, middle temporal fossa, tentorial incisura, and petroclival angle.

Some major pioneers in central skull base surgery pushed neurosurgical community to attempt at maximal if not total removal of these tumors [7–9, 11, 12, 14, 26]. Attempt at radical removal of CS meningiomas is always difficult. It entails the risk of injury or occlusion of the internal carotid artery (ICA) and may aggravate already present cranial nerve deficits or create new ones. At present, general consensus is rather that these meningiomas should be operated on only if they have extracavernous extensions and only these extensions should be excised surgically [3, 26, 36]. As a matter of fact, studies showed a relatively high percentage of damage to cranial nerves when removal of the intracavernous portion of the tumor was attempted [9, 27, 36]. Conversely, leaving a remnant inside the parasellar dural lodge is far from to be frequently followed by tumor growing. In our series of 100 patients in whom only the extracavernous portions were resected and who were followed for long term with Kaplan–Meier statistical analysis, tumor remnants were calculated to remain silent up to 21 years of follow-up in 86.75 % of the cases [36]. In this series, remnant escaping control and requiring reoperation or radiosurgery amounted at 13.25 % [36]. From these data, the authors advised not to systematically do complementary radiotherapy/radiosurgery on the remnant, except for meningiomas of grade III of the WHO classification. For grades 1 and 2, they advocated radiosurgery only if and when growth of the residue is evidenced by imaging survey. Studies confirm efficacy of stereotactic radiosurgery, stereotactic fractionated radiotherapy, or intensity-modulated radiotherapy for control of the residue when regrowth occurs [2, 17–19, 23].

Because central skull base surgery is technically demanding and entails serious surgical risks, detailed neuroimaging investigations are of paramount importance to establish surgical planning. Based on a personal experience on 220-patient series of CS meningiomas in whom resective surgery of the extracavernous extensions was performed, consideration of the role of these imagings in the surgical strategy is the core of this paper.

Imaging

Strategy starts with imaging assessment and is briefly the following. Meningiomas enclosed within the limits of the parasellar lodge, i.e., not transpassing the dural walls, and clinically silent and quiescent at imaging are only watched. Meningiomas enclosed but with symptomatic evolution are proposed as candidates for radiosurgery or preferably stereotactic fractionated modality due to proximity of the visual pathways. In the eventuality of a doubt on the histological nature of the lesion, a percutaneous biopsy through the foramen ovale may be performed prior radiotherapy be indicated [35]. Meningiomas with extracavernous extensions are proposed as candidates for resective neurosurgery.

Magnetic Resonance Imaging (MRI)

MRI represents the basement of the imaging assessment showing the exact location and the various extensions of the meningioma (Fig. 1). Thanks to high contrast resolution, MRI visualizes the tumor's relationships with the ICA and the Willis circle, as well as with the optic pathways, the motor ocular nerves, Meckel's cave with the trigeminal system, also the degree of compression of the pituitary gland, pituitary stalk, and infundibular recess of third ventricle [28]. In addition, MRI depicts the interface between the tumor "capsule" and the adjacent brain tissue and allows to estimate an existence or absence of a well-delineated cleavage plan from the brain parenchyma. Edema or some degree of infarction of the underlying cortical parenchyma would testify invasion of the corresponding pial–cortical vessels [4]. Additional MR angiography gives morphologic information on the degree of displacement, compression, or invasion of the ICA and the principal arteries of the Willis circle without the need of contrast material which is especially useful for patients with allergy to iodine contrast. The same applies for MR venography which is able to show main venous drainages of the cerebral hemispheres to the skull base. These must be taken into account for designing the less risky surgical approach [32, 33].

Computed Tomography (CT)

Thin section CT scan with bone windows is a useful, if not necessary, complement to MRI to delineate meningioma relationships with the neighboring bony structures. It should be systematically studied: anterior and posterior clinoid processes, sella turcica, orbital apex, floor of the temporal fossa, sphenoid wing and its foramens, and petrous apex. It should be systematically searched for invasion of the sphenoid sinus cavities and of the maxillary fossa and also extension to the following key basal structures: the optic canal; the superior orbital fissure; the foramens rotundum, ovale, and spinosum; the intrapetrous carotid canal, and the foramen lacerum (Fig. 2a–c). Sphenoid sinus variations that may complicate CS surgery, such as

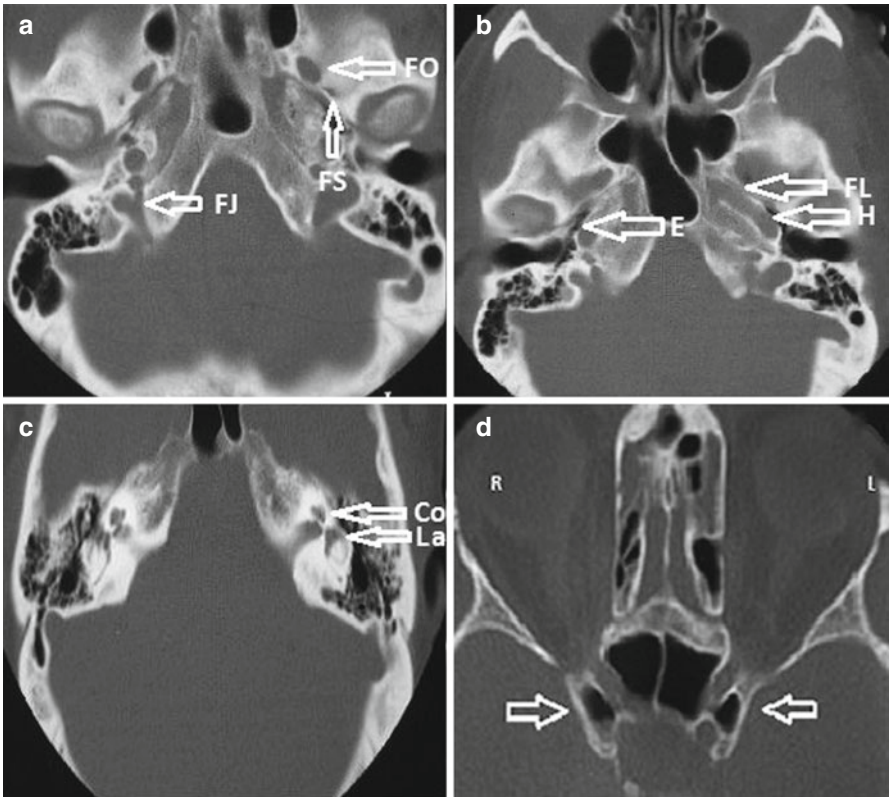

Fig. 2 Thin sections of CT scan with bone windows showing bone anatomy of middle cerebral fossa and petrous bone. (**a**) Foramen ovale (*FO*), foramen spinosum (*FS*), and foramen jugularis (*FJ*). (**b**) Horizontal portion of the intrapetrous carotid canal (*H*), Eustachian tube (*E*), and foramen lacerum (*FL*). (**c**) Cochlea (*Co*) and labyrinth (*La*). (**d**) Sphenoid sinus variations (in another patient) such as pneumatization of the anterior clinoid processes that might complicate surgery, namely, cerebrospinal fluid fistula after drilling (*arrows*)

pneumatization of the anterior clinoid process, can easily be detected by CT scan (Fig. 2d). CT especially with 3D spiral CT reconstruction is prepicious to quantify eventual bony hypertrophy (Fig. 3a) or lysis or invasion of the anterior clinoid process (Fig. 3b) or other bony structures associated with cavernous sinus meningiomas (Fig. 3c). Hyperostoses, because they frequently correspond to tumor infiltration, will be the target of resective drilling [24].

Digital Subtraction Angiography (DSA)

Additional selective four-vessel cerebral DSA via femoral artery brings supplementary informations on the relation of the meningioma with the ICA: its segments and main arterial branches, as well as their degree of invasion (Fig. 4).

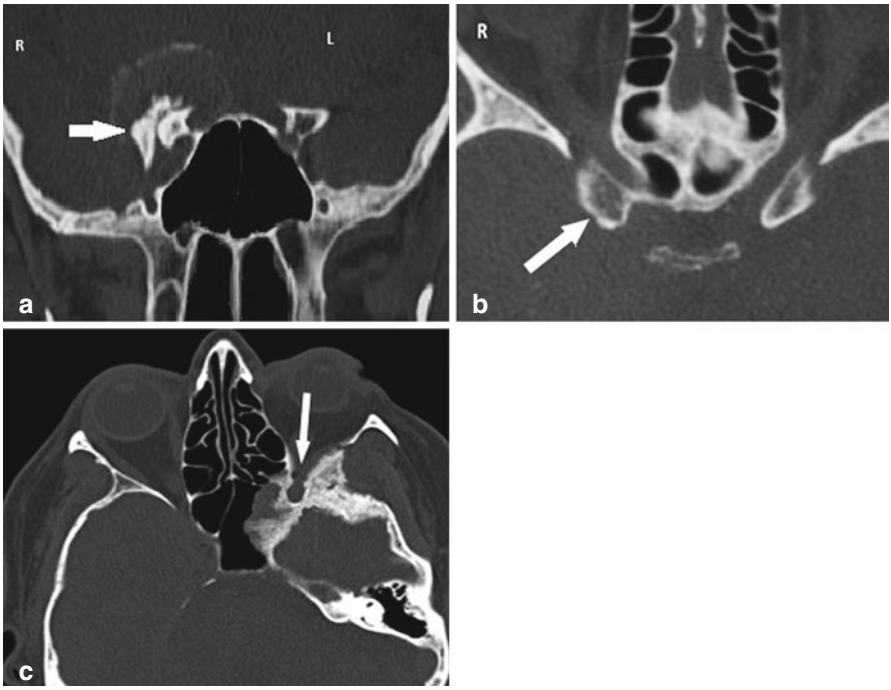

Fig. 3 (**a**) Coronal CT scan with bone windows of a right CS and anterior clinoid meningioma showing hyperostosis of the anterior clinoid process with calcification at meningioma insertion (*arrow*). (**b**) Axial CT scan with bone windows of a right cavernous sinus and orbital apex meningioma showing hypertrophied and invaded anterior clinoid process (*arrow*). (**c**) Axial CT scan with bone windows of a left cavernous sinus and sphenoid wing meningioma showing hyperostosis and invasion of the superior orbital fissure and lateral wall of the sphenoid sinus (*arrow*)

DSA is the only mean to precisely evaluate the fine vascularization of the meningioma and identify its feeders. Feeding arteries arise in various ways from the ICA, its lacerum (C3), cavernous (C4), clinoid (C5), ophthalmic (C6), and communicating (C7) segments (according to Bouthillier's classification) [5], and additionally, frequently, from the ophthalmic artery itself (Fig. 5a, b). Also feeders may come from the middle fossa branches of the external carotid artery (Fig. 5c). Therefore, a selective angiography is useful in studying independently the internal and the external carotid system. Selective DSA also gives opportunity for preoperative embolization of the tumor when the vascularization coming from the external carotid artery is significant. It also permits to evaluate the caliber of the several branches of the external carotid artery for choosing the best donor branch, in the eventuality of the need for an extra–intracranial arterial anastomosis.

Cerebral DSA gives the opportunity to appreciate the capacity of supply of the Willis circle in the eventuality of the necessity of carotid control: by the anterior communicating artery with compression of the contralateral carotid artery at the neck or by the posterior communicating artery from the vertebrobasilar system,

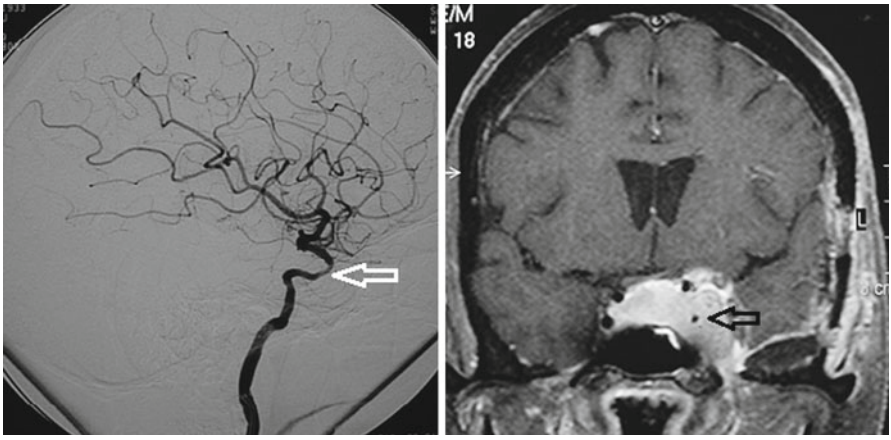

Fig. 4 Relationships of CS meningioma with ICA. Invasion and narrowing of left ICA and its C4 and C5 segments according to Bouthillier's classification (*arrows*). *Left*: internal carotid artery DSA by femoral route in lateral view. *Right*: T1-weighted MRI with gadolinium in coronal section. According to Bouthillier's classification, the *first segment* of the ICA is the cervical segment (C1) which begins at the level of the common carotid artery bifurcation and runs inside the carotid sheath and ends where it enters the carotid canal of the petrous bone; the *second segment* of the ICA is called the petrous segment (C2) which begins at the entrance of carotid canal and ends at the posterior edge of the foramen lacerum; the *third segment* is the lacerum segment (C3) which begins where the carotid canal ends and ends at the superior margin of the petrolingual ligament which runs between the lingula of the sphenoid bone anteriorly and the petrous apex posteriorly; the *fourth segment* of the ICA is the cavernous segment (C4) which begins at the superior margin of the petrolingual ligament and ends at the proximal dural ring; the *fifth segment* is the clinoid segment (C5) which begins at the proximal dural ring and ends at the distal dural ring; the *sixth segment* is the ophthalmic segment (C6) which begins at the distal dural ring and ends just proximal to the origin of the posterior communicating artery; the *seventh segment* is the communicating segment (C7) which begins just proximal to the origin of the posterior communicating artery and ends at the ICA bifurcation

with compression of the ipsilateral carotid artery at the neck during injection of the vertebral artery. In rare occasions, a carotid artery occlusion test with balloon may be performed in the eventuality of a therapeutic ICA occlusion.

Venous phase of DSA is also important to identify major draining veins which sacrifice during approach might cause serious problems, namely, the anterior sylvian, and even more important the inferior cerebral venous drainages, especially the vein of Labbé [15, 33] (Fig. 5d).

Surgical Strategy

This complex of neuroimagings is the basis to deciding the surgical strategy, the type of craniotomy and complementary osteotomy, the usefulness of an anterior clinoidectomy and of a proximal control of ICA at the foramen lacerum, and also the necessity of an extra–intracranial arterial bypass.

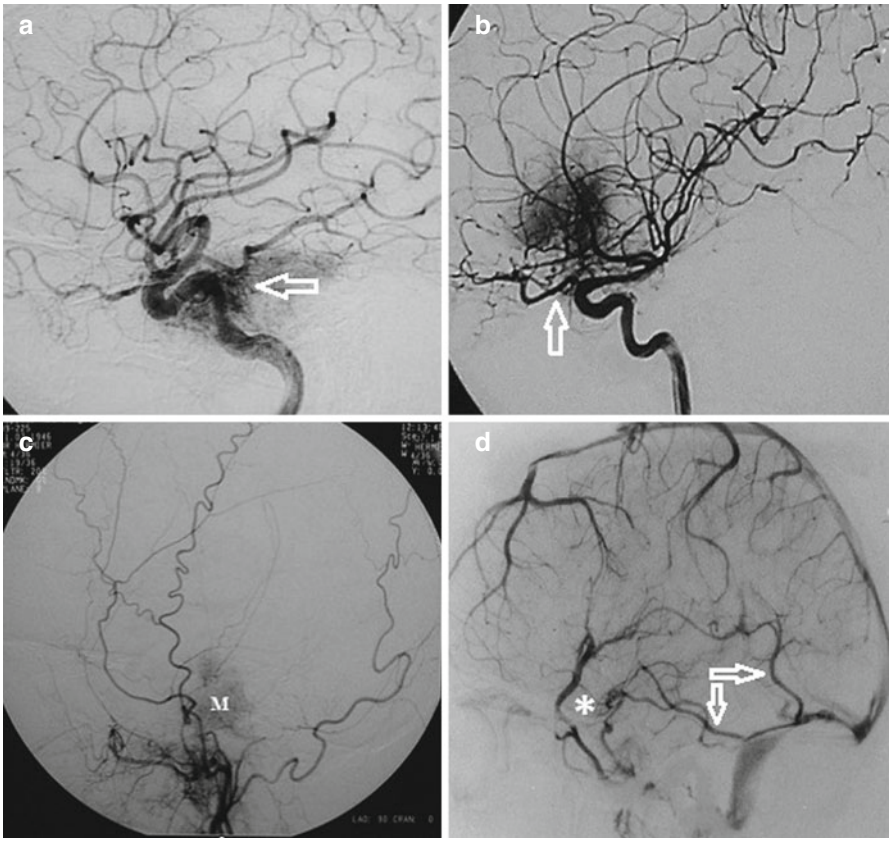

Fig. 5 Selective internal carotid artery (ICA) DSA from different patients (lateral views). (**a**) Selective ICA DSA showing feeding vessels of the meningioma from lacerum segment (C3) (*arrow*). (**b**) Selective ICA DSA showing feeding vessels of the meningioma from paraclinoid ICA and from ophthalmic artery through ethmoidal arteries (*arrow*). (**c**) Selective external carotid artery DSA showing feeding vessels of the meningioma (*M*) from the middle fossa branches of the external carotid artery. (**d**) Venous phase of DSA showing superficial sylvian veins draining anteriorly to the skull base (*asterisk*) and inferior cerebral veins draining to the lateral sinus via the veins of Labbé (*arrows*). Such venous drainages are at risk on cavernous sinus approach and surgery

Surgical approach should permit to have a working zone large enough with multiple angles for attacking the various extensions of the meningioma [34]. In addition, a large multi-angled approach allows to cut vascular supply from the petrous segment (C2), lacerum segment (C3), and paraclinoid and supraclinoid segments (C5 and C6) of the ICA according to Bouthillier's classification [5]. We hypothesized that this strongly contributes to reduce regrowing of the meningioma by means of its devascularization. Also coagulation of the feeders coming from branches of the external carotid artery through the various foramens of the base participates to devascularization at its insertion in the middle cranial fossa.

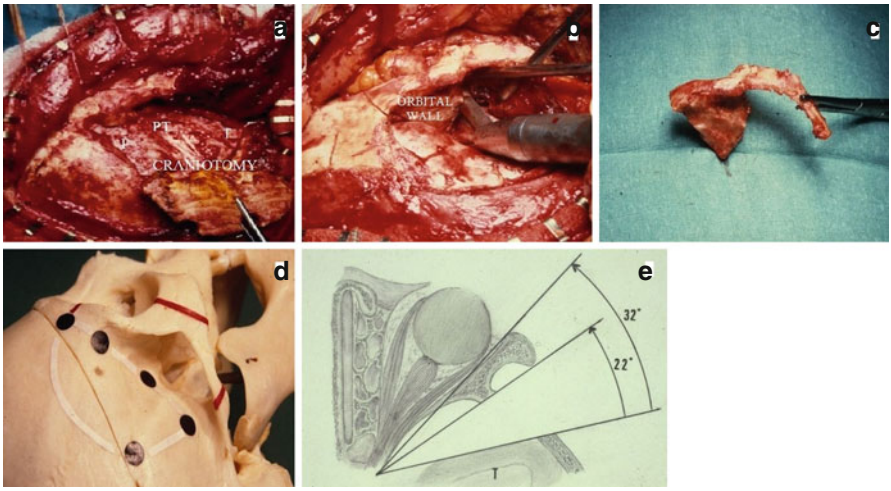

Fig. 6 Surgical technique. (**a**) Pterional craniotomy completed. (**b**) Removal with sagittal saw of the orbitozygomatic arch, together with the superolateral part of the orbital wall. (**c**) Orbitozygomatic bone after osteotomy. (**d**) Landmarks of bone flap and orbitozygomatic osteotomy (OZO). (**e**) Schematic representation of view angle gained by OZO (axial section); OZO gives additional 70 % exposure [1]. OZO facilitates exposure of the superior dome of the tumor when invaginated into the base of the brain (see Fig. 1) and gives different ways to attack the tumor according the concept of "cone of approach" [6]. OZO avoids opening the sylvian fissure and consequently reduces the risk of sacrificing the sylvian venous drainages and also prevents from surgical manipulations of the middle cerebral artery and branches. *F* frontal, *PT* pterional, *T* temporal

Surgical approach should also be determined as such to escape from major morbidity due to excessive retraction of the cerebral parenchyma and sacrifices of the basal draining venous structures [32, 33].

Craniotomy/Osteotomy

Craniotomy is of the frontopterionotemporal type, centered over the sphenoid ridge (Fig. 6a). It is more extended to the frontal side when the meningioma has a predominant suprasellar extension, to the temporal side for cases with a predominant latero-sellar extension and/or extension to the tentorial incisura and the retro-clival region. Opening of the frontal sinus is avoided to prevent from secondary infection risk.

Additional osteotomy (generally orbitozygomatic) is performed when the height of the meningioma is important and its invagination into the base of the cerebrum is pronounced as shown in Fig. 1. Such features are best evaluated on MRI coronal sections. Osteotomy is done with sagittal saw as a second step after performing frontopterionotemporal bone flap (Fig. 6b, c). This osteotomy gives additional 70 % exposure (Fig. 6d, e) and helps to avoid excessive retraction [1].

The cerebral veins of the inferior venous cerebral system of Labbé may limit the subtemporal approach and obliterate pathways to the middle fossa and block approach to the tentorial incisura. These veins have to be recognized prior to surgery to prevent from cerebral infarction. The bony aperture and the way the dura is opened should prevent from stretching and of course avulsion of these veins and unnecessary retraction of the brain which could be infarcted. Knowledge of the venous circulation is a wise precaution prior to surgery [32, 33].

Extradural Approach to the Middle Cerebral Fossa and Proximal Control of ICA at the Foramen Lacerum and Adjacent Petrosal Canal

This part of the procedure is made easy by complementary orbitozygomatic osteotomy. Premier aim is to devascularize the tumor as possible as it can be. According to a recent study on 100 cases of cavernous sinus meningiomas, devascularization of the tumor was likely an important factor inhibiting regrowth of the tumor remnant. As a matter of fact, by surgery alone using this approach, only a minority of the meningiomas (13.25 %) had regrowth from the intracavernous remnant for a follow-up period of up to 20 years according to Kaplan–Meier statistical analysis [36]. Devascularization of the tumor is accomplished by coagulation and division of the middle meningeal artery at the foramen spinosum and also by coagulation with a thin bipolar forceps of the small branches of the external carotid artery which accompany the dural sleeves of the nerves on traversing their foramens at the cranial base, namely: the foramen ovale, foramen rotundum, and the superior orbital fissure (Fig. 7).

Approach of the ICA is at the foramen lacerum, right at the posterior edge of the trigeminal V3 dural sheath before its penetration into the foramen ovale, then posteriorly by unroofing the adjacent portion of the petrous canal (Fig. 8). This permits reduction of the meningioma vascularization coming from the C2 (petrous) and C3 (lacerum) segments of the internal carotid artery (Fig. 8). In most cases, the ICA can be directly reached at the posterolateral border of the foramen lacerum, provided (strong) retraction anteriorly of the dural sheath of V3. Unroofing the carotid petrous canal with rongeur and drill from anterior to posterior should take care not to injure the Eustachian tube and the tensor tympani tendon, laterally, and above all not to open the cochlea by too extensive drilling, posteriorly. The benefit of proximal control of the precavernous ICA at the foramen lacerum is not limited to its contribution to devascularization of the meningioma. This procedure also allows to control the artery in the eventuality of a temporary clamping, in the exceptional situation of an accidental fissuration. Preoperative knowledge of the tumor vascularization, arterial relationships, as well as organization and functionality of the carotid supply from the Willis circle is crucial information.

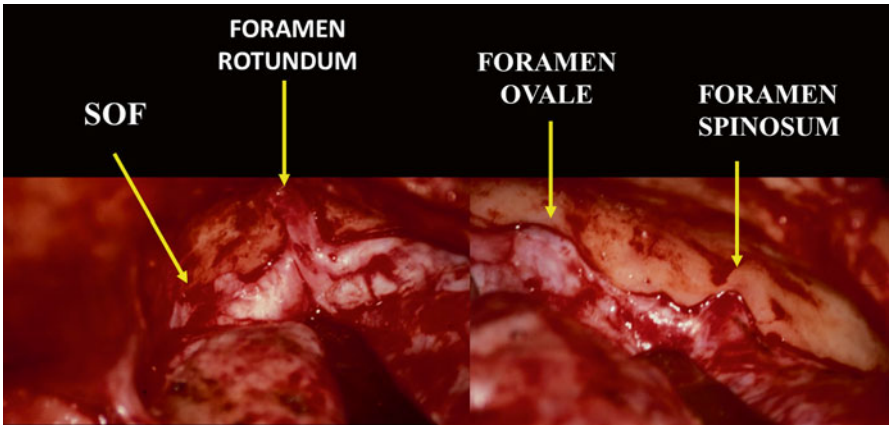

Fig. 7 Operative view of the floor of the middle cerebral fossa, from superior orbital fissure (*SOF*), anteriorly, to foramen spinosum and petrous bone, posteriorly. Right side, extradural exposure after OZO

Extradural Anterior Clinoidectomy and Unroofing of the Optic Canal

Extradural anterior clinoidectomy eases exposure and distal control of the paraclinoid segment of ICA and of the optic nerve (Fig. 9) [10, 22, 38]. Additionally, extradural anterior clinoidectomy is an effective way of reducing the arterial supply coming from the C5 and C6 ICA segments as well as from the ophthalmic artery (as shown in Fig. 5b).

Opening the optic canal together with anterior clinoidectomy is the more important as there are visual disturbances resulting from compression of the optic nerve. This feature is particularly well addressed on thin section CT scan with bone windows, which may clearly show hyperostosis of the clinoid process and/or its invasion with tumor tissue (as shown in Fig. 3b). In addition, soft tumor frequently invades the optic canal along the dural sheath.

Optic nerve decompression by extradural anterior clinoidectomy and optic canal unroofing can be performed without deterioration or even may improve vision, but may also deteriorate it [20, 22]. A recent personal study on 100 meningioma removal cases with extradural anterior clinoidectomy showed 21 % deterioration of homolateral vision after surgery vs. 19 % amelioration on the same side [16]. Actually the role played in visual deterioration by the extradural anterior clinoidectomy procedure itself cannot be firmly established, compared to the role played by the tumor excision, and (sometimes necessary) bipolar coagulation for hemostasis.

Practically, we consider that extradural anterior clinoidectomy is useful, if not necessary, when there is a reduction in the caliber of the optic canal or when the arterial supply of the meningioma is coming mostly from the paraclinoid segment of the ICA and the ophthalmic artery. An alteration in visual acuity and/or campimetry at preoperative examination pleads for attempting at decompression of the optic nerve.

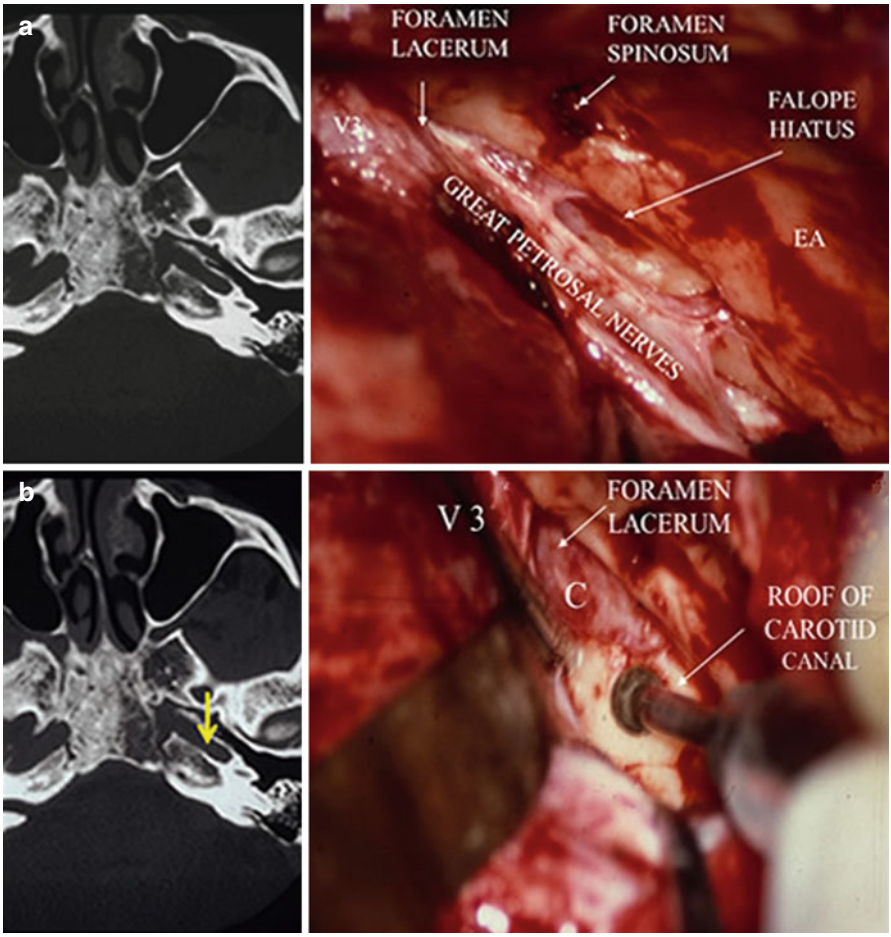

Fig. 8 Steps for accessing ICA at foramen lacerum and horizontal portion of the petrous carotid canal. Operative views through extradural subtemporal approach, on the right side. (**a**) After coagulation and division of the middle meningeal artery at foramen spinosum, the great petrosal nerves are exposed at their exit from Falope hiatus. These nerves correspond to the landmarks of the horizontal portion of the carotid canal and the Eustachian tube. *EA* eminentia arcuata. (**b**) The posterior edge of the foramen lacerum is reached underneath the V3 dural sheath, after exerting strong anterior retraction. Then, the carotid artery is exposed by unroofing the carotid canal from anterior to posterior, using a small rongeur and/or a diamond drill (*arrow* = horizontal ICA petrous canal). (**c**) Such an approach is able to provide an approximately 1 cm exposure of the ICA, which would allow a temporary clamping if necessary. A laterally extended drilling skeletonizes the Eustachian tube. The Eustachian tube is separated from the ICA by a thin but marked bony wall (*arrow*), which lodges the tendon of insertion of the posteriorly oriented tensor tympani. (**d**) Skeletonizing Eustachian tube is not necessary; if so as shown in the operative view it must not be effracted to avoid secondary obstruction responsible for serous otitis

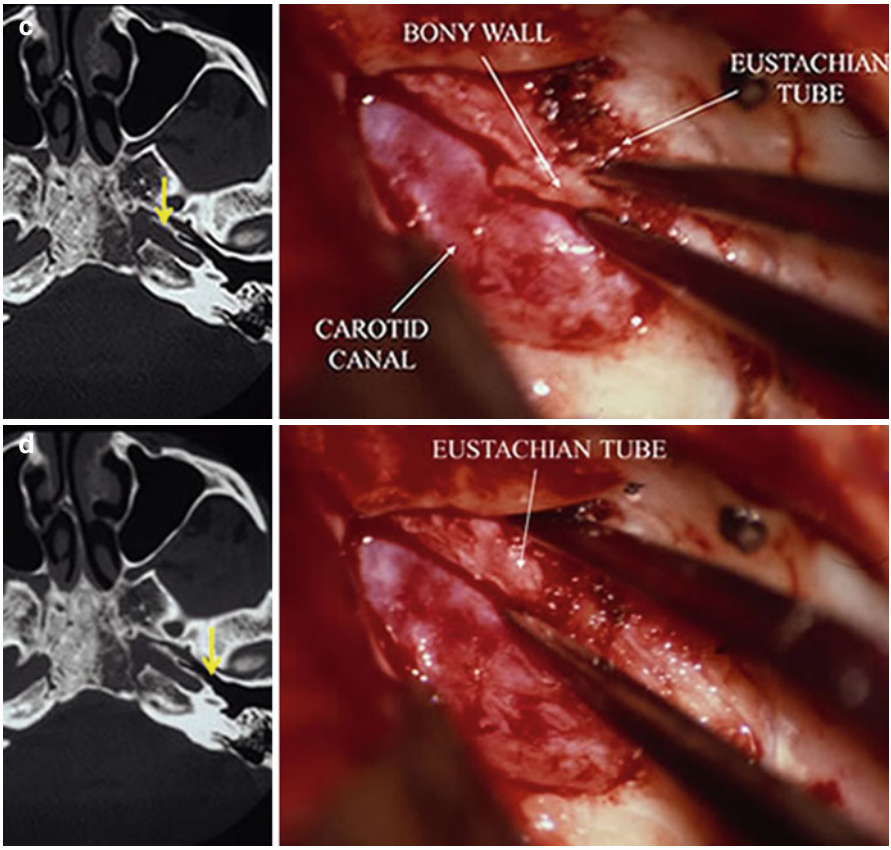

Fig. 8 (continued)

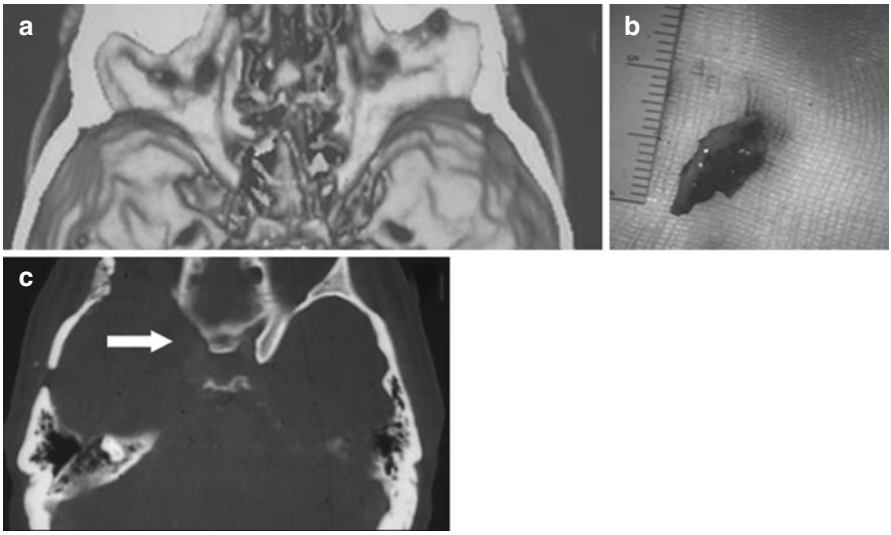

Fig. 9 (**a**) 3D CT scan. (**b**) Anterior clinoid process extracted in one piece through extradural approach. (**c**) CT scan with bone windows (axial section) showing anterior clinoidectomy associated to unroofing of optic canal (*arrow*)

Extra–Intracranial Arterial Bypass

Extra–intracranial arterial bypass would be an essential part of CS meningioma surgery if the aim would be total removal including intracavernous portion. Since current consensus is to limit surgery to the resection of only the extracavernous portion(s), extra–intracranial arterial bypass is not indicated excepted in the cases with severe stenotic invasion of the internal carotid artery and/or the middle cerebral artery, when supply by the Willis circle is not functional. When done, we performed between the superficial temporal artery (mostly its posterior branch) and a cortical branch of the middle cerebral artery (mostly the gyrus angularis artery), because of its simplicity and lesser risks. When such an extra–intracranial bypass is planned, the approach should start by dissecting the superficial temporal artery and protect it until anastomosis is completed. A high flow transcranial bypass using autografts such as the saphenous vein or the radial artery can be preferred, as the modern tendency [6, 25, 37].

Removal of the Extracavernous Portion(s) of the Meningioma Through Intradural Way

Dural incision is performed along a semicircular line centered at pterion over the sylvian fissure. The dural flap which base is on orbital side is reflected and fixed over the periorbital periosteum. This is especially important in the eventuality of an orbital wall resection to avoid postoperative enophthalmus. According to extension of meningioma along the tentorial incisura, additional subtemporal incision of the dura mater can be done but not extensively to prevent from avulsion of the inferior cerebral veins of Labbé.

CS meningiomas which have suprasellar extension invaginating to the base of the brain, as shown in Fig. 1, may benefit orbitozygomatic osteotomy combined to the frontopterionotemporal craniotomy to facilitate the tumor dome exposure [1]. Such an additional osteotomy provides the possibility to have different trajectories to attack the tumor, according the concept of “cone of approach” [21, 29, 30]. Enlarged corridors permit to reach with less retraction the optic nerve and the optic chiasm, the carotid artery as well as the posterior communicating and anterior choroidal arteries medially, and also the oculomotor and trochlear nerves posteriorly. Osteotomy of the orbitozygomatic arch, because it provides a shorter and wider access to the parasellar region, allows in most cases to avoid opening the sylvian fissure and therefore sacrificing the superficial sylvian veins and manipulating the middle cerebral artery and branches [13, 31, 34].

The first step for tumor resection is to reach the lateral wall of the cavernous sinus, then posteriorly tentorial incisura. From back to front and from base to up, the trochlear and oculomotor nerves, the P2 segment of the posterior cerebral artery, the posterior communicating artery and its branches, the anterior choroidal artery, and the

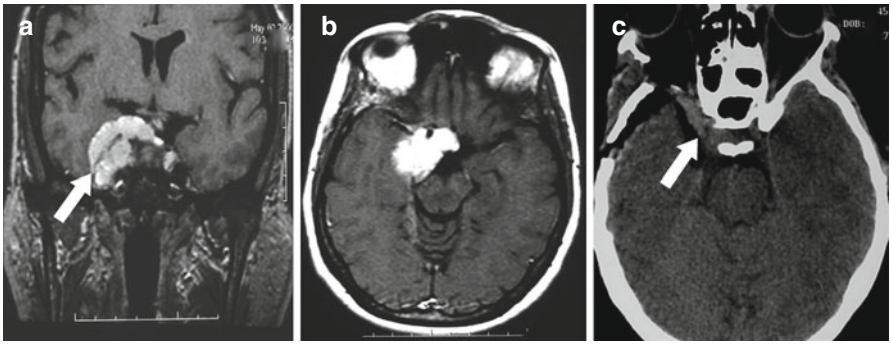

Fig. 10 T1-weighted MRI with gadolinium (coronal and axial sections) showing right cavernous sinus meningioma with latero- and suprasellar extension. (**a**) On coronal section, the lateral wall of the parasellar lodge is quite delineated (*arrow*), and it should not be transpassed during tumor resection. (**b**) Axial section showing tumor extension into the (right) suprasellar cistern and willis circle. (**c**) Axial section of post-op CT scan showing the remnant located inside the lodge

optic tract are identified and dissected free. If there is a soft extension into Meckel's cave, its roof is opened and gasserian ganglion dissected free. If more extended resection is desired, incision of the tentorial incisura is performed; then, trigeminal root is dissected and freed. Tentorial incision permits visualizing the petroclival region down to Dorello's canal through which the abducens nerve passes and also the basilar artery and superior cerebellar artery, posteriorly and medially. Because the trochlear nerve is on the way and constitutes a fragile obstacle, the nerve should be identified before incisura is divided and the underneath fragment attacked and extracted.

Most accepted consensus is that excision of the tumor should be limited to its extracavernous extension(s). Excision is done piecemeal with bipolar coagulation, and additionally with ultrasonic aspirator if the tumor is hard. The lateral dural wall and the roof of the cavernous sinus should not be transpassed; this is most often possible as they are generally identifiable if care to this barrier is taken (Fig. 10). The suprasellar extension is attacked through the classical following triangles (Fig. 11): retrocarotidian, optico-carotidian, and interoptic, until pituitary stalk is reached and freed.

Decompression of the oculomotor and trochlear nerves inside the lateral wall of the CS can be additionally performed, from the cavernous sinus roof to the superior orbital fissure, by incising the outer layer of the CS lateral wall and freeing the nerves there. But it should be emphasized that aggressive dissections and extensive coagulations of these nerves may aggravate or create new deficits.

At the end of resection, small pieces of fat tissue, taken from the thigh at the same time as fascia lata harvested for dural closure, are inserted between the CS roof and the vascular and nervous structures of the adjacent basal cisterns, and between the CS lateral wall and the mesial aspect of the temporal lobe (Fig. 12). Such fatty "plan of protection" aims at limiting invasion of adjacent cisterns by the intracavernous remnant, deliberately left in place. This also may help to delineate the target in the eventuality of complementary radiosurgical treatment. Late imaging control shows that the fat persists long term [36]. We speculated that this fat tissue

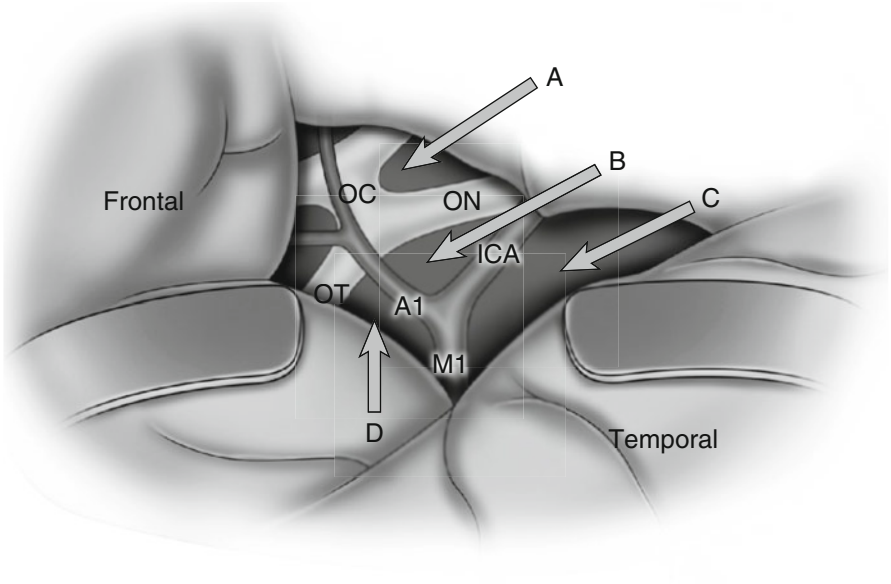

Fig. 11 Schematic drawing of basal cisterns through right pterional approach. The CS suprasellar extensions should be attacked successively through the following triangles: retrocarotidian (*C*), optico-carotidian (*B*), and interoptic (*A*) until pituitary stalk is reached and freed. *D* A1-M1 (anterior) perforating space, *ON* optic nerve, *OC* optic chiasm, *OT* optic tract, *ICA* internal cerebral artery, *A1* anterior cerebral artery, portion 1, *M1* middle cerebral artery, portion 1

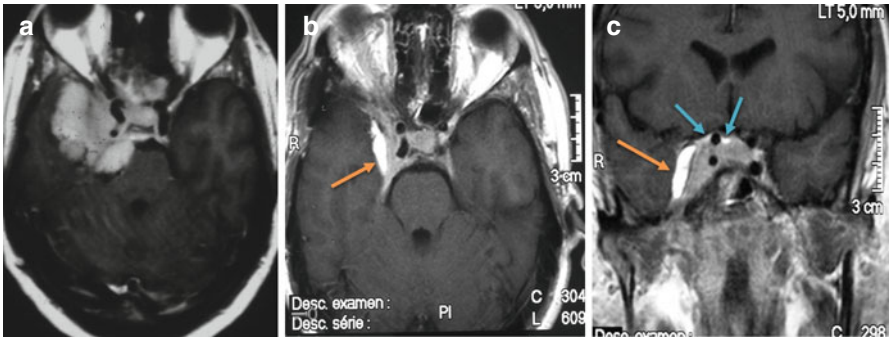

Fig. 12 Pre- and post-op MRI of right CS meningioma with large extensions. (**a**) Pre-op T1-weighted MRI with gadolinium (axial section) showing supero- and latero-sellar extension of the meningioma and also extension to petroclival region. (**b**, **c**) Same patient's post-op T1-weighted MRI with gadolinium (**b**, axial section; **c**, coronal section) after resection of the extracavernous extensions. Thin small pieces of fat tissue (taken from the thigh, at the same time as fascia lata) are put between the roof of the cavernous sinus and the vascular and nervous structures of the basal cisterns, and between the lateral wall of the cavernous sinus and the mesial aspect of the temporal lobe (*arrows*). Such "layer of protection" might limit invasion of the cisterns and adjacent structures by the parasellar remnant. It has been confirmed by late imaging control that this fat long term persists [9]. In addition, this may help to delineate the target in the eventuality of complementary radiosurgical intervention

can play a role in "limiting" regrowth of the residual intracavernous tumor by making a barrier for angiogenesis from adjacent structures; indeed, only 13.25 % of the 100 meningiomas who underwent surgery alone in our series, and were followed for up to 20 years according to Kaplan–Meier analysis, regrew [36].

Conclusion

Because of their location in a region occupied by important vessels and nerves and in close vicinity with the visual pathways and hypothalamo–hypophyseal tract, CS meningiomas are difficult tumors to deal with. At present, general consensus is that these meningiomas should be operated on only if they have extracavernous extensions, and only these extensions should be excised surgically.

Detailed imaging is able to provide surgeons almost all necessary informations that can be converted into practical decisions for establishing an optimal surgical strategy. MRI with high resolution shows relationships of extensions with the surrounding basal structures and visualizes ICA involvement. Thin CT sections with bone windows delineate invasions of the skull base bony structures. DSA via femoral route brings supplementary informations on the fine vascularization of the meningioma and its arterial feeders, and also the intracranial circulation and its supply.

Complementary orbitozygomatic osteotomy avoids extensive opening of the sylvian fissure and brain retraction with its risk of avulsion the inferior cerebral veins. Extradural approach of the middle cerebral fossa with proximal control of the ICA at the foramen lacerum as well as extradural anterior clinoidectomy and unroofing of the optic canal with control of the ICA paraclinoid segment make surgery safer. In addition, clinoidectomy deprives the meningioma from its feeders from the ICA and the ophthalmic artery.

When resecting the extracavernous portion(s) of the tumor, the dural walls of the CS should not be transpassed, not to increase or create cranial nerve palsies or injuring the intracavernous ICA. Extensive coagulations may aggravate cranial nerve deficits. If and when growing, the intracavernous remnant can be controlled by complementary radiosurgery and stereotactic fractionated radiotherapy.

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Optic Pathway Gliomas

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Contents

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Abstract Optic pathway gliomas (OPGs) are among the most challenging neoplasms in modern pediatric neuro-oncology. Recent technological advances in imaging, surgery, and chemotherapy may lead to better understanding of the pathophysiology and better clinical results. This chapter reviews these advances and the current treatment paradigms.

Keywords Optic Pathway Glioma • OPG • Neurofibromatosis 1 • NF1 • Low-grade glioma

Introduction

Optic pathway gliomas (OPGs) are among the most challenging neoplasms in modern pediatric neuro-oncology. Recent technological advances in imaging, surgery, and chemotherapy may lead to better understanding of the pathophysiology and better clinical results. This chapter reviews these advances and the current treatment paradigms.

Definition and Classification

Optic pathway gliomas are low-grade glial neoplasms (WHO grade I) that originate from any location along the visual system such as the optic nerve (ON), optic chiasm (OC), optic tracts (OT), and, rarely, the optic radiation (OR). Figure 1 demonstrates various OPG presentations. The term OPG represents a wide spectrum of anatomical variations. These lesions tend to have an erratic natural history, requiring careful follow-up and management by a multidisciplinary team. In addition, age, coexistence of NF1, histology, and molecular markers may be important factors in the clinical behavior and in the practical individualized decision-making process. The subset of patients seen by the pediatric neurosurgeon may be biased towards the aggressive end of the spectrum, with a tendency to progress and require multiple treatment lines.

Several different classification methods have been developed for OPG. Dodge introduced the first method of classification in 1958 [26]. The Dodge system classifies OPGs into 3 classes, based on the anatomical location of the tumor (Fig. 2). Tumors of the ON are termed Dodge I, tumors of the chiasm are Dodge II, and posterior tumors, or those that extend into nearby structures, are Dodge III. This method, defined in the pre-CT and pre-MR era, is still widely used, mainly for research purposes. However, its clinical relevance is limited.

The modified Dodge classification system, developed in 2008 [93], is a more detailed anatomical classification, breaking down each component into several highly precise categories. The modified Dodge also takes into account additional factors such as the existence of NF or leptomeningeal dissemination [93]. This method, while very precise anatomically, is probably too complicated to be routinely implemented in clinical patient care. Another drawback of both Dodge classification methods is the lack of sensitivity to indications of tumor progression.

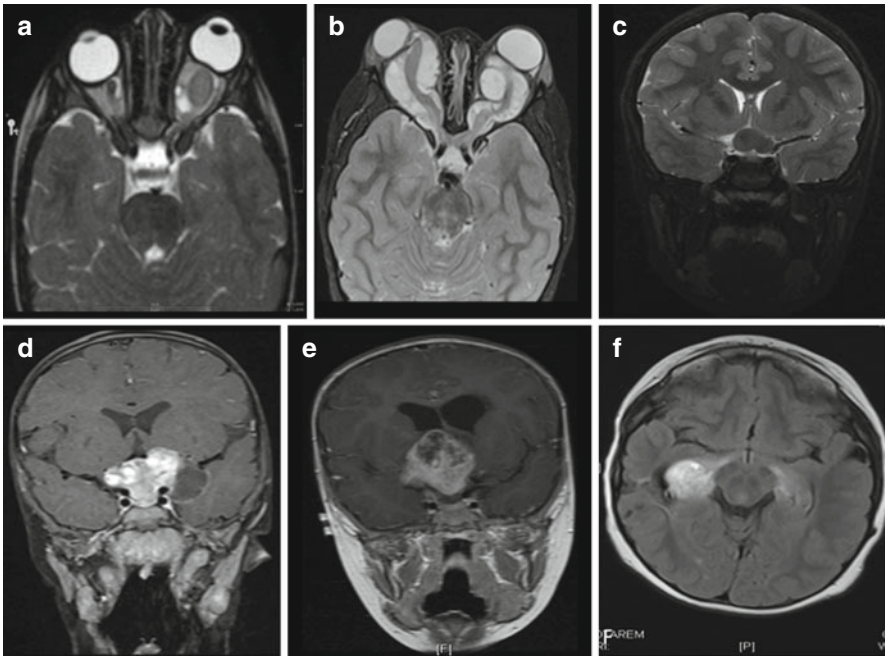

Fig. 1 Various OPG presentations. (**a**) Isolated optic nerve glioma of the left ON. (**b**) Bilateral ON glioma involving the chiasm. (**c**) Chiasmal glioma with no involvement of the hypothalamus. (**d**) Large chiasmal glioma involving the hypothalamus with a cystic component. (**e**) Large chiasmatic/hypothalamic glioma that compresses the third ventricle, causing hydrocephalus. (**f**) Posterior glioma of the optic radiations

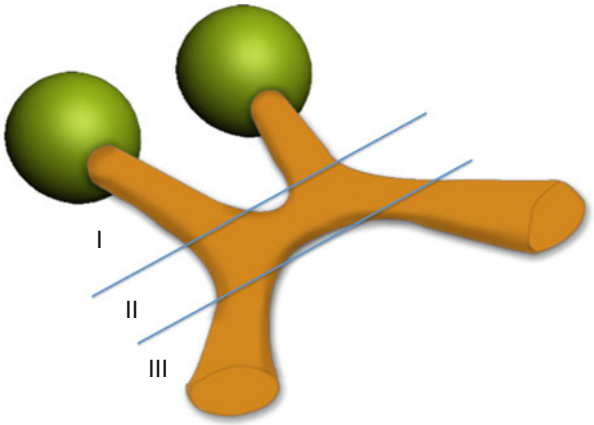

Fig. 2 Schematic representation of the 1958 Dodge classification system. *I* ON glioma, *II* Chiasmatic glioma, *III* posterior glioma or chiasmatic with involvement of extra optic structures

Table 1 Our proposed new anatomical classification system for OPG

Nerve	Chiasm	Posterior	General
1 – Mid thickening	1 – Chiasm confined	1 – Focal involvement	Cyst: Yes/no
2 – Severe thickening	2 – Chiasm and hypothalamus	2 – Extensive involvement	Hydrocephalus: Yes/no
Enlarged ONSD: Yes/no	3 – Chiasm and 3rd ventricle		Other CNS Malignancies: Yes/no
Tortuous ON: Yes/no	4 – Major superasellar involvement		Diffuse NF related changes: Yes/no
Pressure on globe: Yes/no			Age at presentation?
Enhancement: Yes/no	Enhancement: Yes/no	Enhancement: Yes/no	Favorable molecular properties?
Isolated involvement: Yes/no	Isolated involvement: Yes/no	Isolated involvement: Yes/no	

A third classification system that attempted to address the issue of functional status was suggested by Fred Epstein in 1985 [65]. This classification system is based on an evaluation of two components, tumor/anatomical and functional. The *tumor component* is rated into one of four classes (T1: one ON, T2: both ONs, T3: OC, and T4: hypothalamus/thalamus). The *functional component* is rated into one of 5 classes (V0: normal; V1: impaired, one eye; V2: impaired, both eyes, or blind, one eye; V3: blind, one eye and impaired, one eye or field defect; and V4: blind both eyes).

Other factors that should be considered when attempting to stage an OPG patient are the presence of NF1, the age at diagnosis, symptoms at presentation, and the risk of hydrocephalus. We have therefore suggested a new morphologic classification that utilizes recent advances in imaging and may aid in clinical management and patient stratification (Table 1 and Fig 3).

In NF1 patients, caution is warranted when attempting to classify OPGs. Despite the fact that this is a relatively common tumor in NF1 patients, there are many radiological abnormalities that may complicate the diagnosis. An example of such misleading abnormalities are T2 hyperintensities that sometimes have mass effect, and focal signal changes within the ON that may either be preneoplastic or without any significance.

Epidemiology

OPGs are relatively rare neoplasms, comprising ~1 % of all CNS neoplasms in the general population and ~5 % of CNS neoplasms in children [84]. The annual incidence (as reported in the pre-MR era) is 1/100,000 [5]. The real number is probably

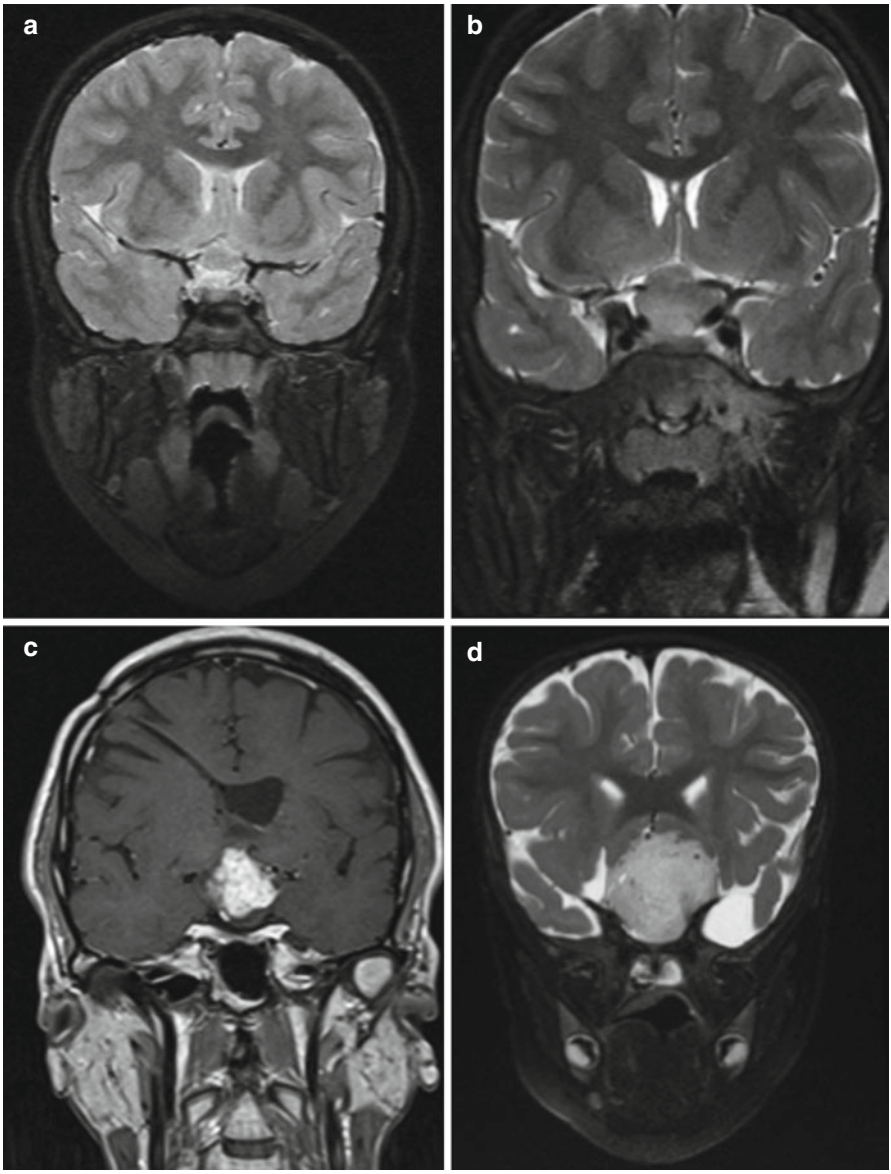

Fig. 3 Four different classes of chiasmatic/hypothalamic glioma. (**a**) Chiasmal thickening only. (**b**) Chiasm and hypothalamus. (**c**) Chiasm and third ventricle involvement. (**d**) Major suprasellar involvement

higher. Eighty percent of all diagnosed patients are in the first decade of their lives, and 90 % are in the first two decades. The mean age at diagnosis is 8.8 years in older series, ranging between 2.7 and 5.4 years in more recent series [38, 94, 96]. An estimated 37 % of OPG tend to progress [61]. There is no gender predisposition. In a large series

published recently by Nicolin et al., 58 % of 133 OPG patients were NF1 positive. The mean age at diagnosis in this series was 5.9 years, 50 % of the tumors were hypothalamic chiasmatic, 60 % were diagnosed based on imaging only, and 52 % required treatment over the course of a follow-up period of 9 years [68]. The high proportion of Dodge II/III tumors in this series may be attributable to a referral bias.

OPG and NF1

Bilateral OPGs are considered pathognomonic for NF1 and are one of the diagnosis criteria of NF1. The co-occurrence of NF1 in an OPG patient is considered a good prognostic factor [61, 64]. In a recent series comparing NF1 OPG to sporadic gliomas, children with NF1 had a significantly better clinical picture at diagnosis, with less increase in intracranial pressure, less decrease in visual acuity, and fewer abnormalities of fundus of the eye. Radiological progression, visual deterioration, and endocrinological damage were also less frequent in NF1 OPGs.

OPGs appear in almost 30 % of NF1 patients and may present with a variety of radiological and clinical changes [13]. In NF1 patients, the lesion tends to be located anteriorly and involves only a single nerve when compared to generic OPG patients [18]. The spectrum of imaging appearance in NF1 patients is broad, ranging from fine signal changes on T2-weighted MRI, through enlarged optic nerve sheath, up to gross optic nerve tumors and chiasmatic lesions that protrude into the third ventricle or other neighboring structures. When considering posterior tumors in NF1 patients, it is important to remember that they may easily be confused with NF-T2-hyperintensities that may be expansile and have a mass effect. Careful radiological and clinical follow-up is warranted before making any therapeutic decisions for lesions of the optic radiations. Historically, NF1 OPGs were considered relatively indolent tumors that do not tend to progress. Recently, several publications have described a more active clinical course, with progression of the tumor noted in up to 75 % of NF1 patients, even in children older than 11 years old [42]. Recently, macrocephaly was also correlated with OPG existence in NF1 patients [83]. In addition, in a genetic study targeting genotype-phenotype correlation done by Sharif et al., an NF1 patient with OPG was found to have a 6.05 odds ratio to have the NF1 mutation in the 5′ tertile end of the gene when compared to an NF1 patient with no OPG [86].

OPG in Adults

Adult OPGs can be divided into two groups; adult patients with tumors diagnosed in childhood (usually low grade), and adult patients diagnosed during adulthood (usually high grade). In our center, we summarized the data of 22 adult OPG patients. Age distribution at OPG diagnosis varied widely (6 months–66 years), as

did age at last follow-up (18–74 years). Ten patients were diagnosed at adulthood, the remaining 12 in childhood.

Of the patients who were diagnosed at childhood ($n = 12$), 6 had radiological progression during childhood and 3 of those suffered visual impairment. From this group of 6 patients who displayed radiological progression in childhood, one patient had further radiological progression during adulthood accompanied by additional visual decline. Two patients had additional visual decline during adulthood even though there were no signs of radiological progression. The other three patients seemed to stabilize, displaying no additional radiological progression or visual impairment. Of the 6 patients whose tumors were stable or improved (regressed) during childhood, all 6 remained stable with no radiological progression or visual decline in adulthood.

Of the 10 patients diagnosed at adulthood, 6 patients suffered visual deterioration during the follow-up period; in 5 out of these 6 a concomitant radiological progression was noted. Two of the adult-diagnosed patients were diagnosed with high-grade gliomas; both died of their disease.

Eleven patients were diagnosed with NF1, 7 at childhood and 4 at adulthood. Six out of the 7 NF1 patients diagnosed at childhood experienced stable disease with no visual decline, both as children and as adults. Similarly, 3 out of the 4 NF1 patients in the adult-diagnosis group experienced stable disease with no visual decline.

OPGs may be stable or active during childhood or adulthood. As a general rule, patients with radiologically stable tumors diagnosed during childhood did not suffer progression during the follow-up period. Prolonged follow-up should be considered for patients who suffered visual decline or radiological progression during childhood, as well as for late-onset adult OPG patients. OPG is a possible cause for visual decline in adult NF1 patients.

Several practical implications arise from our data. Our experience leads us to recommend prolonged follow-up for pediatric OPG patients who suffered visual decline or radiological progression in childhood, even after a period of stability. In addition, early intervention and more aggressive management may be necessary for adults diagnosed with LGG of the optic pathway. Adults with HGG of the optic pathway demonstrated more favorable prognosis than their counterparts with more commonly located tumors in our limited series.

Clinical Presentation

Visual complaints are the mainstay of clinical symptoms and signs, although may be hard to detect due to the young age of these patients. These include decreased visual acuity (VA), nystagmus, and proptosis, and are found at presentation in 46 % of patients.

Neurological problems, such as headaches, vomiting, and seizures, are present in only 16 % of patients [1]. These low percentages are attributed to the high percentage of patients who are diagnosed during routine screenings, especially in NF1 patients. The diagnostic age for patients with sporadic (non-NF related) OPGs is

older than for NF1 patients. This is mainly attributed to the fact that diagnosis occurs only after clinical symptoms appear and not on routine screening, as in the NF1 population [38].

Mode of presentation varies with the anatomical location of the tumor. Posterior tumors are associated with endocrine dysfunction, such as precocious puberty, and with hydrocephalus. Anterior tumors are associated more with visual abnormalities [1]. Visual signs, such as cranial nerve III/IV/VI palsy, papilledema, and optic atrophy, are present in a minority of cases. Visual deficit usually correlates with the tumor location; posterior tumors may cause hemianopia while unilateral ON tumors will cause monocular visual impairment [59]. It is important to remember that assessing visual field in OPG maybe a difficult task due to cooperation difficulties. In our series of 19 patients treated with chemotherapy, visual field was assessable in only 35 % of patients at diagnosis [88]. Signs and symptoms of raised intracranial pressure should be taken seriously, since acute hydrocephalus has been reported as a presenting symptom. Diencephalic syndrome (cachexia, macrocephaly, nystagmus, and visual deficit) is seen in 21 % of infants with chiasmatic/hypothalamic tumors [2].

Diagnostic Studies

Radiology

Today, the gold standard for OPG diagnosis is MRI. To maximize diagnostic yield, MR protocols should be planned with the assistance of an experienced neuroradiologist and should include orbit-directed scanning with fat suppression and contrast injection.

Tractography, the use of diffusion tensor imaging (DTI) MR pulse sequence for the assessment of white matter tracts, is a promising tool [6]. This method was utilized in two studies to assess tumor-induced changes in OPG. In these studies, the OPG caused fibers to either end abruptly within the tumor mass, or induce abnormalities in the arrangement of the visual white matter tracts [29, 62]. Identification of abnormally displaced fibers using this method may also aid in presurgical planning and assist in preserving visual function. The relevance of these changes to the individual patient is still not clear.

Tumors may differ in MR appearance depending on their locations, but they are usually isointense on T1, hyperintense on T2, receive variable enhancement, and have cystic as well as solid nonenhancing components. Tumors of the ON usually do not have cystic changes, appearing as gross thickening of the nerve itself, with or without nerve sheath enlargement. The differential diagnosis for ON enlargement is broad, including meningioma, neuroma, hemangioblastoma, and lymphoma [44]. Optic nerve sheath enlargement is found in nonneoplastic diseases such as increased intracranial pressure, optic neuritis, Grave's disease, sarcoidosis, toxoplasmosis, central vein occlusion, idiopathic intracranial hypertension, and tuberculosis [76, 87]. Posterior tumors may appear as minimal chiasmal thickening, or as large masses

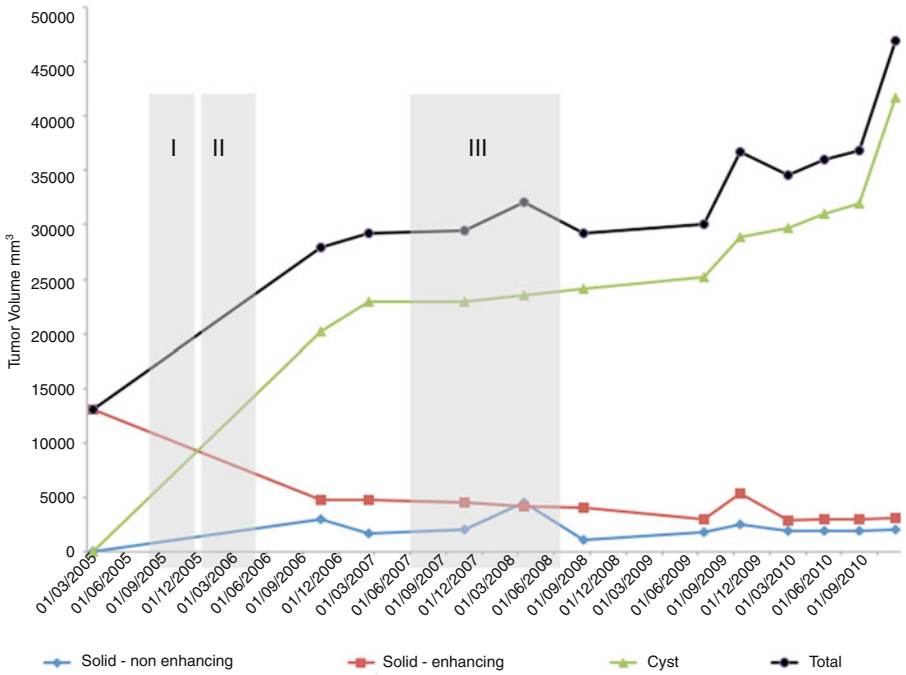

Fig. 4 Volumetric follow-up of one of our patients with internal segmentation into three components and integrated treatment periods. Note that despite the fact that the gross total tumor volume enlarges, there is a marked reduction of the sold component following chemotherapy. The main progression is of the cystic component. *Total* gross total volume of the tumor, *Solid-enhancing* volume of the enhancement receiving bulk on MR imaging, *Solid-nonenhancing* volume of the solid portion of the tumor that does not receive contrast enhancement on MR imaging, *Cyst* volume of the cystic component on MR imaging, *I* treatment period with vincristine and carboplatin, *II* treatment period with vinblastine, *III* treatment period with rapamycin and tarceva

protruding into the third ventricle with apparent mass effect. Cystic changes are common and are a part of the natural history of the tumor. Neoplastic changes posterior to the lateral geniculate nucleus are rare and are difficult to differentiate from NF1 T2 hyperintensities. Unfortunately, initial radiologic appearance does not correlate with visual prognosis. We have found deteriorating vision in patients with tumors that seem to be stable anatomically, as well as stable vision in patients whose tumors demonstrated structural progression. Recently, it has been suggested that dynamic contrast enhancement may correlate with progression, with larger mean permeability values in aggressive tumors [50].

Due to the long follow-up required in these patients and the importance of early detection of changes in the tumor bulk or in its internal components, we recommend the use of volumetric measurements. These measurements, although time-consuming, may improve patient care by enabling more accurate decision making [89, 97]. Figure 4 demonstrates a volumetric follow-up of one of our patients; some of the corresponding MR images are presented in Fig. 5.

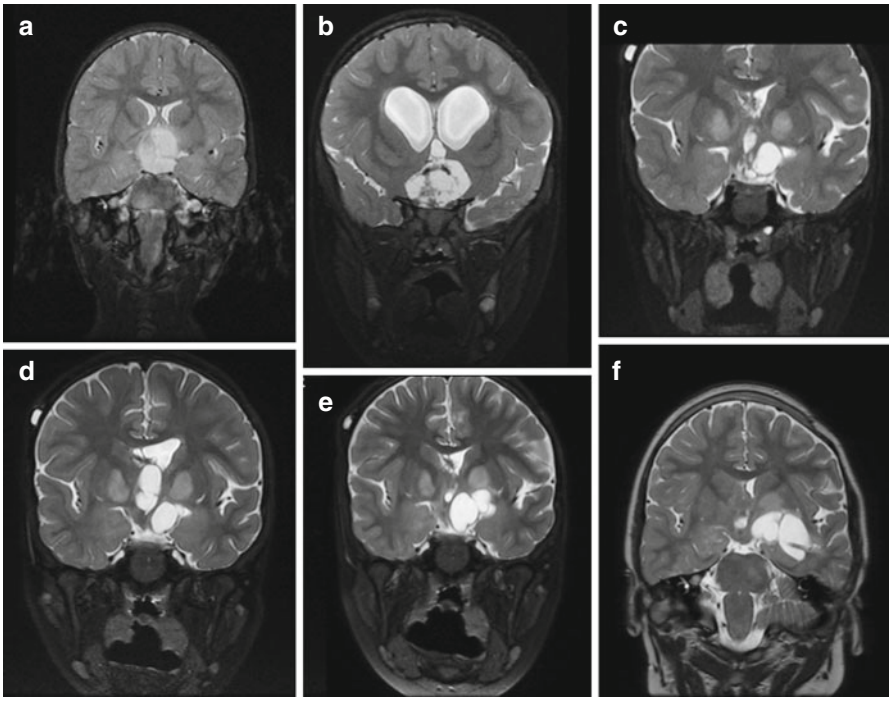

Fig. 5 Anatomical history of a chiasmatic/hypothalamic glioma. Serial coronal T2 images of a 4-year-old boy with NF1 who presented with visual deterioration [**a**-**f**]. Within 4 years, a deterioration to bilateral blindness occurred despite three different chemotherapy treatment lines. Note the cystic changes that the tumor undergoes

Ophthalmology

Neuro-ophthalmology is crucial for both diagnosis and follow-up of OPG, as visual decline is the potentially worrisome consequence of the tumor. Neuro-ophthalmological evaluation is often difficult, especially in young patients where cooperation is limited [8]. A decline in visual acuity is often present at diagnosis and sometimes may be the reason for initial testing, even in the very young (e.g., an infant that starts bumping into objects or sitting closer to the television). In addition, color vision, visual field, eye movements, relative afferent pupillary defect, pupil size, and fundus should all be evaluated. Any progressive change should be considered seriously as a reason to initiate therapy. In very young children, a normal exam does not rule out visual impairment from an OPG. Optical coherence tomography (OCT) has been shown to detect loss of retinal nerve fiber layer in children with OPG (Fig. 6). This may prove to be an auxiliary tool in the diagnosis of visual damage in young children, as well as providing evidence regarding visual reserve and need for treatment [10, 17].

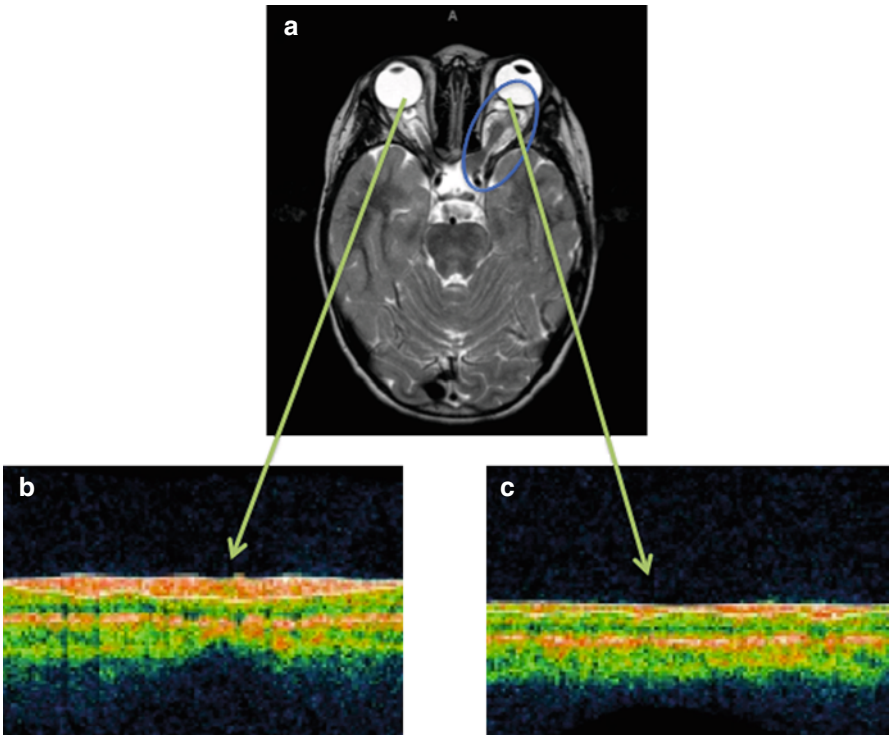

Fig. 6 NF1 OPG patient (**a**) with an ON tumor on the left nerve (*blue circle*), Optical Coherence Tomography (OCT) of the right, normal eye (**b**), and of the left, tumor-affected eye (**c**) (*green arrows*). This patient had a VA of 20/20 on the unaffected (right) eye and 20/400 on the tumor-affected eye. VA correlated well with retinal nerve fiber lair thickness of 105 μm on the right (normal) vs. 48 μm on the left (severely thinned) (Images courtesy of Dr. Robert Avery, Children's National Hospital, Washington DC)

Endocrine

Endocrine assessment should be done in any child with chiasmatic/hypothalamic glioma. Endocrinological abnormalities such as central precocious puberty and growth hormone deficiency are detected in approximately 20 % of OPG patients. Endocrine symptoms may even precede neuro-ophthalmological signs [92]. It should be noted that growth hormone deficiency is present in approximately 2.5 % of NF1 patients even without OPG [19].

Pathology

OPGs are typically low-grade glial neoplasms. Pilocytic astrocytoma (PA) accounts for the vast majority of these tumors. The rest usually consist of fibrillary and pilomyxoid astrocytomas (PMA), oligodendrogliomas, and gangliogliomas. Most

of the confirmed pathologies discussed in the literature are usually either PA or PMA. PMA usually present in younger patients, showing a pattern of progression, local recurrence, and seeding through CSF pathways. In a series published by Komotar et al., PMAs were associated with a mortality rate of 33 %, almost twice as much as the numbers for PA (17 %) in this series. In addition, PMAs are also associated with decreased odd survival [3, 52]. A more aggressive behavior pattern may be predicted for labeling indexes such as high ki67 [32, 84] as well as PMA histology [28, 52]. One of the molecular and genetic factors that differentiate PA from PMA is the underexpression of the *ALDH1L1* gene, occurring in 89 % of PMA and known to occur in phenotypically aggressive PA [79]. P53 mutations and variable activation of the hedgehog pathway may also be a feature of PMA [3, 81]. Malignant transformation of low-grade OPG is rarely seen; most frequently associated with irradiation [99].

Natural History and Prognosis

OPGs have an erratic natural history. Some of these tumors progress, others are steady for a lifetime, and others spontaneously regress [77, 80]. This has led to the theory that OPGs are not a single entity, but rather a group composed of two or even three subtypes that are often hard to distinguish from one another. These subtypes vary widely in their clinical and radiological outcome. While some OPGs undergo spontaneous regression, there is a significant group of large chiasmatic/hypothalamic tumors that tend to progress and even metastasize. Figure 5 demonstrates a progressive OPG of the chiasmatic/hypothalamic type over 4 years of follow-up.

Interestingly, out of the 5 % of low-grade gliomas that undergo leptomeningeal spread, OPGs represent ~50 % [33]. Before this behavior pattern was recognized, these tumors were sometimes considered benign, even hamartomatous in nature [45], requiring only careful follow-up. OPGs are now perceived as progression-prone, persistent tumors that pose a major therapeutic dilemma. As many as 35 % require treatment at presentation [68]. Patients who do not require treatment at initial presentation have varying chances for progression. Those with NF1 have only 15 % likelihood of progression, while sporadic OPG patients have up to 75 % probability of progression.

Molecular analysis of tumor tissue shows promising early results in predicting the course of the disease. In particular, the BRAF-KIAA 1549 fusion protein seems to indicate tumors with a tendency to arresting growth and even prone to spontaneous senescence. In a recent study, 5-year PFS was 61 %+−8 % for B-K fusion positive patients and 18 % for negative patients. In this study, 61 % of generic OPG were B-K fusion protein positive and no NF1 related OPG was positive for this mutation [41]. Although not currently utilized in routine clinical practice, we believe that this analysis should be considered for any non-NF1 patient in whom therapeutic decisions are made based on radiological progression only.

Treatment

The follow-up and management of OPG requires an experienced multidisciplinary team that provides individualized patient care. Only then can adequate therapeutic decisions be made. The goal of treatment is to prevent visual decline and to achieve long-term tumor control. In the presence of a severe mass-effect or hydrocephalus, immediate, life-saving neurosurgical procedures may be indicated. In most cases, however, OPGs are not a life-threatening tumor. The risk to benefit ratio of treatment must therefore be considered carefully for each patient.

The exact timing of treatment initiation is one of the major open questions in OPG management. In most cases, we recommend delaying treatment for as long as possible unless a clear-cut radiological progression or visual decline is noted. Treating an asymptomatic or minimally symptomatic stable patient seems to offer no advantage over observation alone [7, 32, 96]. Thus, current guidelines suggest intervention *only* when there is a documented decline in vision or radiological progression [61]. Treatment initiation dilemmas may be very relevant to a child, especially an infant, who presents for the first time with compromised vision. At the moment of presentation, progression cannot be defined. However, compromised reserve may be a relevant reason to start treatment earlier, rather than later.

We recommend imaging and neuro-ophthalmological examinations (including visual field and OCT if available) every 6 months. Patients with compromised reserve for whom a decision was taken not to treat should be clinically examined more frequently. If the tumor is chiasmatic/hypothalamic, a detailed endocrinological evaluation should be performed. If the patient has been stable for a period of a year and has no adverse prognostic factors, follow-ups may be scheduled on a yearly basis.

The choice between treatment options such as surgery, chemotherapy, and irradiation is not easy and depends on the team's experience and biases. The following sections outline general rules for these treatment modalities. Figure 7 illustrates a suggested management algorithm for OPG.

Biopsy

For tumors with characteristic MRI appearance that are epicentered on the optic pathway, especially in an NF1 patient, no biopsy is required [60]. Biopsies are indicated if the tumor has an atypical appearance on MR, for an unusual age group (older than 10 years old or younger than 1 year old), or with unusual clinical characteristics (rapidly progressing or severe neurological deficits other than vision loss). When biopsy is indicated, tumor topography dictates the preferred technical method. When the ventricular system is expended, an endoscopic approach can be used to combine multiple procedures, including biopsy, septum pellucidotomy, and accurate shunt placement [21, 22]. Otherwise, a stereotactic needle biopsy can be performed for larger lesions, either with a frame or by frameless techniques [74].

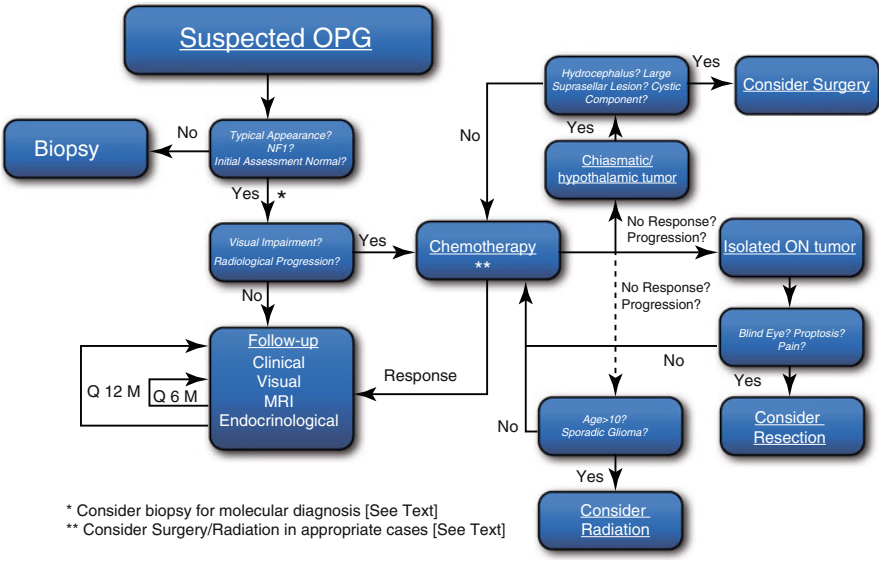

Fig. 7 Management algorithm for OPG patients. *ON* optic nerve; see text for specifics

Smaller lesions must occasionally be approached openly through standard microsurgical techniques, or by basal transsphenoidal techniques when the tumor fills the sella turcica. It has been argued that the mere knowledge that an OPG has pilomyxoid characteristics is important for early treatment decisions. The value of a biopsy of an OPG for molecular diagnosis is still controversial. The example of the bRAF mutations, provided previously, may represent only the beginning of a long awaited breakthrough. Biopsies may be useful for molecular diagnosis of tumor characteristics that may have prognostic or therapeutic consequences [41, 75, 95]. These analyses, although not yet included in routine clinical practice, are proving valuable and we expect them to be essential for therapeutic decisions and estimating prognosis in the near future.

Surgery

Clinical series describing surgical results for OPG are usually comprised of small patient numbers, with vague inclusion criteria, no control groups, and poor follow-up. The current situation includes wide variations between different centers and groups with regard to the threshold for open surgery.

Tumors confined to the optic nerve are considered for resection if they show progressive proptosis or intractable pain in a blind eye. These tumors can be approached via unilateral frontal craniotomy and orbitotomy or through the eye,

especially when enucleation of the entire eye is warranted. Globe-sparing-resection is also possible. It should be noted that sectioning the nerve close to the chiasm risks damage to the advancing nasal fibers (Wilbrand's knee) from the contralateral eye.

Surgical management of chiasmatic/hypothalamic tumors is even more controversial. Different microsurgical techniques have been proposed for the removal of large OPG. These different approaches depend primarily on the individual topography of the tumor. Radical resection in a patient with viable eyesight is usually not recommended due to the susceptibility of the surrounding neural structures (hypothalamus and brainstem). In addition, there is a high risk of damage to the optic apparatus and vascular structures [98]. Subtotal resection of tumors that grow outside the visual system, such as the third ventricle, anterior, and lateral subarachnoid spaces, can be performed for a subset of large suprasellar lesions [30]. In addition, subtotal resection may have a beneficial effect on visual outcome via selective decompression of the optic apparatus [90] and may even cause long-term tumor control in selected patients and lessen the hypothalamic dysfunction that is usually associated with more radical resection [43, 98].

Chiasmatic/hypothalamic lesions may be approached via interhemispheric transcallosal, subfrontal pterional, subtemporal, or bifrontal interhemispheric translamina terminalis routes, depending on the direction and the extent of the tumor. Combination approaches may also be used for more extensive lesions. In a surgical series presented by Goodden et al. in 2010, a transcallosal approach was safely used in nine patients with large exophytic tumors that were either causing obstructive hydrocephalus or progressing on serial scanning. Significant debulking (>50 %) was achieved in ~70 % of patients with no incidence of visual deterioration [36]. Image-guidance facilitates accurate navigation and avoidance of damage to critical structures. Hydrocephalus may respond to decompression alone, but in many cases may also require shunt placement, which is usually the preferred method [82]. Ascites secondary to ventriculoperitoneal shunting in chiasmatic tumors is common and may require diverting CSF to the atrium rather than to the abdomen [35]. Large cystic components containing mucinous fluid are common and may require multiple resections and drainages. Shunts placed within these cysts tend to malfunction after a short period of time; Ommaya reservoirs may be used in these situations for intermittent tapping and drainage.

Chemotherapy

Chemotherapy is considered the first line of treatment in most cases of children with progressive OPG.

"Gentle Chemotherapy" with vincristine and carboplatin was introduced in 1987 by Packer et al. and is now an accepted first-line treatment [71]. This regimen reported PFS rates of 75 % at 2 years and 68 % at 3 years for chiasmatic tumors [71]. Carboplatin alone may also be effective in OPG treatment, with a short-term PFS rate of 83 % and disease stabilization in 85 % [4]. Weekly vinblastine is also frequently used as first line or in patients with carboplatin allergies [58]. Recently,

a new protocol of bevacizumab and irinotecan has shown preliminary effectiveness in the treatment of recurrent low-grade gliomas [72]. Temozolomide was suggested as a possible option for second- or third-line treatment with an overall disease stabilization rate of 54 % in patients with progressive OPG [40].

Adverse effects of chemotherapy vary according the regimen and drugs used. Among the side effects of the vincristine and carboplatin protocol are carboplatin-associated allergies occurring in ~10 % of treated patients [73], and peripheral neuropathy. Hematological side effects such as neutropenia and thrombocytopenia may occur with this protocol, but are usually associated with nitrosourea-based regimens [78]. Temozolomide was shown to cause grade 2–4 thrombocytopenia and neutropenia in ~23 % of treated pediatric OPG patients in addition to intratumor hemorrhage in ~3 % [40].

Mammalian target of rapamycin (mTOR) is an important part of the ras pathway, which is hyperactivated in NF1 and is considered a potential target for inhibition. However, experiences to date with protocols that include mTOR inhibitors such as Tarceva and Rapamycin have been only mildly effective [70]. Clinical trials with other mTOR inhibitors such as RAD001 (Everolimus) are currently underway.

Several papers published in recent years have shown disappointing results for the visual outcome following chemotherapy for optic pathway gliomas [14, 23, 88]. In many patients, despite some success in achieving structural tumor control, there was no improvement and even further decline in visual ability. Others, such as Fisher et al., have provided somewhat better results for visual prognosis with chemotherapy treatment, but only for a relatively short follow-up time, providing results only after first line chemotherapy and for NF1 patients only [31].

In addition to anatomical tumor response, chemotherapy has shown benefits in preserving intellectual function when compared to radiation, and in controlling diencephalic syndrome [39, 57].

Radiation

With the establishment of chemotherapy as the first-line treatment of choice for low-grade gliomas in general, and for OPG specifically, the use of radiation has lessened significantly. The long-term negative consequences of radiation, especially in young patients and even more so in the NF1 population, have made radiation an alternative to be used only as a last resort.

In children younger than 3 years old, radiation is contraindicated due to unacceptable cognitive impairment. In older, non-NF1 children, radiation may be effective for OPGs that are progressive despite chemotherapy, for metastatic tumors, or for unresectable tumors. With the usual dose of 45–60 Gy in 1.6–2 Gy fractions, 5-year PFS and overall survival rates are reported to be in the range of 82–85 % and 93–94 %, respectively [27]. A modest beneficial effect on visual ability has also been reported [15, 37]. Recently, in a series of 20 patients from St. Jude (ages 3–14 years), all treated with conformal radiation therapy as an adjuvant therapy,

a beneficial effect on VA was shown for previously operated patients and not in patients who received chemotherapy [11].

The main reason for discouraging radiation therapy for OPG is the multiple long-term adverse effects. These are especially apparent in the NF1 population. In the generic OPG population, even children over 3 years old who received radiation therapy experienced cognitive side effects [53, 54]. Endocrine dysfunction occurs in 39–55 % of irradiated patients [37, 53–55]. In a large series of 69 patients treated before the chemotherapy era, published by Cappelli et al. in 1998, ~15 % of irradiated patients suffered from cerebrovascular complications. In the same series, ~30 % of patients irradiated at a young age suffered severe intellectual disabilities [15]. In the NF1 population, the two main long-term effects of radiation are moyamoya syndrome (MMS) [12] and secondary CNS malignancies [85]. In a series of 28 irradiated patients described by Kestle et al., 5 (18 %) developed MMS. In this same series, 60 % of NF1 patients developed MMS [51]. Secondary malignancies (such as malignant peripheral nerve sheath tumors) occur in 50 % of NF1 OPG patients who undergo irradiation, as opposed to 20 % of patients who do not receive irradiation. There is an increased relative risk (threefold) for the irradiated NF1 OPG group [85]. In addition, irradiation tends to induce anaplastic changes in the original glial tumor. In one series dealing with low-grade gliomas, 16 % of irradiated patients developed anaplastic changes, as opposed to none in the group that did not receive radiation [25].

Recently, Stereotactic Radiosurgery (SRS) was tested as a possible treatment for OPG with some promising results. In several small series, good tumor control was achieved, improvement in vision was noted, and side effects were rather small [20, 24]. Some of the serious adverse effects associated with radiation may be technique dependent, and the further examination of newer, safer techniques is warranted, especially when considering the rather low efficacy of chemotherapy in improving and preserving visual ability. Gamma knife and proton beam therapy may also prove to be useful tools in the future [46, 56, 66].

Outcome

OPG outcome is generally favorable. Long-term survival rates are excellent, ranging between 80 and 96 % in numerous series over the last 10 years [1, 32, 68]. In an older series from 1993, the overall 10-year survival rate was 84 %, with anterior tumors (nerve and chiasm) having a 10-year survival of 95 % and posterior tumors 76 % [49]. PFS rates vary, considered around 50 % depending on location, background, and the need for treatment. In the same series from 1993, PFS at 10 years was 80 % for tumors of the nerve and chiasm and 59 % for tumors spreading outside the chiasm [49].

From our own experience, ~25 % of OPG patients referred to a tertiary center require therapy; out of this group ~75 % will need to receive second-line treatment [88]. These numbers, higher than the accepted numbers in the literature, are probably

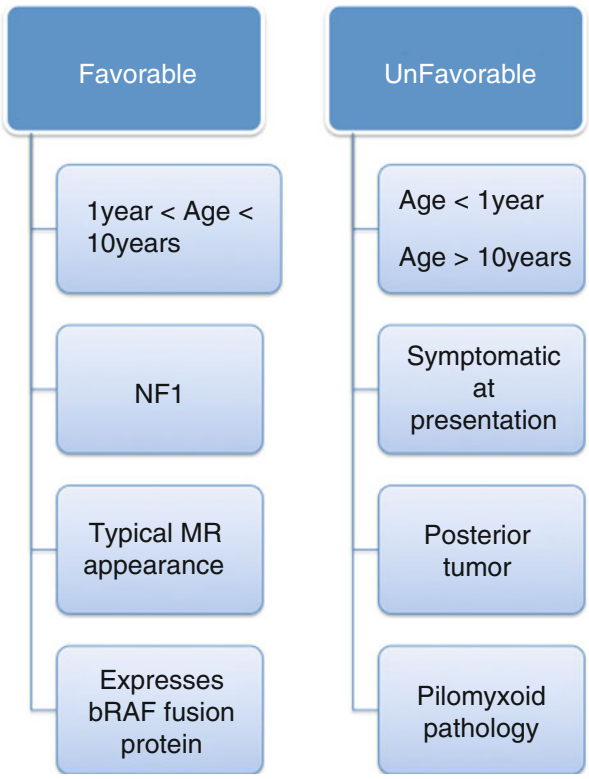

Fig. 8 Favorable and unfavorable prognostic factors

biased due to the more aggressive nature of the tumors seen by a pediatric neurosurgeon. Various factors described in the literature as having an effect on prognosis [69] are summarized in Fig. 8.

Preservation of vision is the primary goal in the treatment of OPG. It is now clear that there is only poor correlation between radiographic changes and visual outcome [31, 68, 88]. Therefore, visual acuity (VA) is the recommended outcome measure for treated OPG patients [8]. At diagnosis, approximately 30 % of the patients are already experiencing visual impairments of varying magnitude [14, 34]. According to Fisher et al., in a multicenter retrospective study looking at 115 NF1 OPG patients receiving initial treatment with chemotherapy, 32 % experience improvement in their VA, 40 % stabilize, and 28 % experience further deterioration [31]. However, several other studies have also dealt with the overall visual outcome of treated OPG patients [14, 23, 67, 88]. In these studies, although numbers are limited, there was no significant beneficial effect of chemotherapy on visual outcome.

Aside from the visual outcome, there are other issues related to the general health and quality of life in OPG patients. Among them are endocrinological outcome, neuropsychological status, and secondary malignancies.

The long-term endocrinological status of OPG patients depends on several factors. Among them are location of the tumor, surgery, and previous radiation treatment. Surgery and radiation tend to worsen endocrinological function, which can be disrupted to some extent in 40–100 % of patients, depending mostly on the location [1, 43, 47, 48, 91]. In addition, late progression of the tumor itself also causes endocrinological impairment that can range from panhypopituitarism to single hormone deficiency such as growth hormone. Patients may require hormonal replacement therapy and often will not reach expected weight and height [48, 91].

Secondary malignancies (both solid and hematologic) occur in approximately 10 % of all OPG patients [43, 49]. They may occur spontaneously in approximately 20 % of patients with NF1-associated OPG. NF1 patients are highly sensitive to ionizing radiation. When irradiated, the percentage of secondary malignancies rises to approximately 50 % of patients [85], although only a third of the secondary malignancies are located in the irradiation field [54]. This sensitivity must be a major consideration in modern treatment choices, forcing a strong preference for chemotherapy over radiation. It is yet to be determined whether modern radiation techniques (such as 3D planning and proton beam therapy) and better candidate selection can significantly reduce this potentially devastating complication. Note that many other factors may also contribute to the formation of secondary malignancies, such as chemotherapy treatment and the individual's susceptibility to oncogenic processes. The exact role of each of these factors in this process is yet to be determined.

Neurocognitive decline is evident in 35–40 % of OPG patients, especially in children younger than 5 years old at diagnosis [15, 32, 48]. Neurocognitive deficits are present as a baseline in NF1 patients. The exact role of OPG as a possible indicator of higher NF burden or increased susceptibility to neurofibromin deficit in non-NF1 OPG patients and the relationship with the neurocognitive phenotype is unknown. Evidence in the literature regarding the effect of treatment on long-term neurocognitive outcome, and the role the basic disease takes in this process, is inconsistent [16, 32].

The big difference between long-term survival and progression free survival, as well as the heterogeneity of the patients, makes long term of follow-up of OPG patients necessary. In addition, the discrepancy between functional outcome and anatomical outcome makes estimating an individual OPG patient's outcome even more difficult [63].

Conclusion

The goal of visual control in OPG has not yet been reached. Further understanding of the different OPG subgroups, and the underlying pathophysiology of visual loss, is required to effectively and individually treat these patients. Large multicenter prospective studies aimed at examining new treatment modalities are desperately needed to improve this front (Table 2).

Table 2 Recommended articles and important clinical series

Reference	Type	Summary
Lacaze E et al., *Br J Cancer*, 2003 [57]	Clinical series	Series of 27 treated patients evaluated for neuropsychological outcome. It shows that chemotherapy as first line preserves intellectual outcome by avoiding or delaying radiation
Opocher E et al., *Eur J Cancer*, 2006 [69]	Meta-analysis	Systematic literature review summarizing 11 studies for prognostic factors. Age < 1 year is a clear and independent prognostic factor. NF1 and tumor site may also play a role
Listernic R et al., *Ann Neurol*, 2007 [61]	Review	Comprehensive review coupled with expert opinion of the NIH NF1 OPG task force. Focusing on NF1-associated OPG. Includes a list of evidence-based management guidelines
Massimi L et al., *Expert Rev Anticancer Ther*, 2007 [63]	Review	Very comprehensive review of the recent advances and challenges in the management of OPG patients
Nicolin G et al., *Pediatr Blood Cancer*, 2009 [68]	Retrospective series	Retrospective series of 133 (78 NF1) children with OPG. There was no difference in PFS between chemotherapy versus chemotherapy + debulking or debulking alone. PFS for the NF1 patients who required treatment was similar to that of non-NF1 patients
Sharif S et al., *J Med Genet*, 2011 [86]	Genetic study	A genetic study aimed at finding a genetic factor for development of OPG in NF1 patients. A mutation located in the 5′ tertile end of the gene has an OR of 6.05 in OPG patients when compared to non OPG NF1 patients
Avery RA et al., *J Neurooncol*, 2012 [9]	Visual outcome-focused review	Describes VA assessment in children with OPG and proposes a standardized VA testing protocol for future pediatric OPG clinical treatment trials
Awdeh RM et al., *Int J Radiat Oncol Biol Phys*, 2012 [11]	Prospective clinical series	Assesses VA prospectively in 20 OPG patients after conformal radiation therapy. Found that patients initially treated with chemotherapy prior to receiving radiation therapy have decreased visual acuity compared with those who receive primary radiation therapy
Fisher MJ et al., *Neuro Oncol*, 2012 [31]	Retrospective multicenter study	Retrospective series of 115 NF1 OPG patients treated with first-line chemotherapy. At completion of treatment, VA improved (32 % of subjects), remained stable (40 %), or declined (28 %). There is poor correlation between radiographic and VA outcome

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Minor and Repetitive Head Injury

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Abstract *Traumatic brain injury* (*TBI*) is the leading cause of death and disability in the young, active population and expected to be the third leading cause of death in the whole world until 2020. The disease is frequently referred to as the silent epidemic, and many authors highlight the "unmet medical need" associated with TBI.

The term traumatically evoked brain injury covers a heterogeneous group ranging from mild/minor/minimal to severe/non-salvageable damages. Severe TBI has long been recognized to be a major socioeconomical health-care issue as saving young lives and sometimes entirely restituting health with a timely intervention can indeed be extremely cost efficient.

Recently it has been recognized that mild or minor TBI should be considered similarly important because of the magnitude of the patient population affected. Other reasons behind this recognition are the association of mild head injury with transient cognitive disturbances as well as long-term sequelae primarily linked to repeat (sport-related) injuries.

The incidence of TBI in developed countries can be as high as 2–300/100,000 inhabitants; however, if we consider the injury pyramid, it turns out that severe and moderate TBI represents only 25–30 % of all cases, while the overwhelming majority of TBI cases consists of mild head injury. On top of that, or at the base of the pyramid, are the cases that never show up at the ER – the unreported injuries.

Special attention is turned to mild TBI as in recent military conflicts it is recognized as "signature injury."

This chapter aims to summarize the most important features of mild and repetitive traumatic brain injury providing definitions, stratifications, and triage options while also focusing on contemporary knowledge gathered by imaging and biomarker research.

Mild traumatic brain injury is an enigmatic lesion; the classification, significance, and its consequences are all far less defined and explored than in more severe forms of brain injury.

Understanding the pathobiology and pathomechanisms may aid a more targeted approach in triage as well as selection of cases with possible late complications while also identifying the target patient population where preventive measures and therapeutic tools should be applied in an attempt to avoid secondary brain injury and late complications.

Keywords Traumatic brain injury • Imaging • Biomarkers • Endocrine consequences • Repetitive • Mild

Introduction

Mild traumatic brain injury (mTBI) is a special entity with ill-defined characterization and stratification as well as unclear short- and long-term consequences. This is the typical topic where increasing knowledge brings about more questions than

answers. Nevertheless, the magnitude of the injured population as well as the bulk of evidence that points to the significance of repeated insults should explain why this disease entity has been attracting more and more attention recently.

It is obvious that a chapter like this cannot provide sufficient information about all aspects of such a controversial topic, and to explore the field in its entire depth should be well beyond the scope of this work. Our primary goal is to highlight the most important and/or controversial aspects of mTBI while also focusing on ongoing/emerging research topics and areas.

Definition, Epidemiological Data

Traumatic brain injury (TBI) imposes a public health problem worldwide due to its high incidence and often severe long-term consequences [41]. Even in mild traumatic brain injuries (mTBI), totaling up to 80–90 % of TBI cases, every third injured undergoes prolonged physiological or neuropsychological complications, and long work-off times are common [25].

A consensus definition claims that TBI is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force." It is a significant cause of mortality and morbidity in adults [89] and is the leading cause of death in childhood [136]. According to the Centers for Disease Control and Prevention (CDC), approximately 1.7 million Americans sustain a TBI each year and of those 75–90 % are classified as minimal or minor. This makes mild TBI (mTBI) more common than stroke, multiple sclerosis, and Huntington's disease combined, giving it the sad primacy of the most frequently occurring brain disorder [2]. In addition, mild TBI has also been called the "signature injury" of the conflicts in Iraq and Afghanistan, potentially affecting several thousands of US soldiers, the majority from blast exposure [56].

During the past few decades, there has been a better understanding of the more subtle functional and cognitive deficits that may result from TBI [137] and an increasing recognition of the impact of mild TBI that resulted in an attempt to clarify diagnostic criteria for this disease entity [128].

Unfortunately, conventional imaging such as CT, T1, and T2 MRI are usually not able to detect the underlying pathology; the vital role of these methods is to rule out lesions that need emergent neurosurgical treatment [166]. Thus, missing a specific marker for mTBI, often the patient's self-report and subjective complaints are the only available data to rely on.

Therefore, the wide heterogeneity of definitions and nomenclature of mild head injuries is not surprising.

To this end, it is of note that the terms "mTBI" and "concussion" ("commotio cerebri") are interchangeable and are frequently used this way (*vide infra*). The most accepted elements of mTBI diagnosis at admission are GCS (Glasgow Coma Scale) of 13–15, LOC (loss of consciousness) < 30 min, and PTA (posttraumatic amnesia) < 24 h[93] (Table 1).

Some groups suggest normal CT scan as additional criteria for mTBI [93]. Others use the term "complicated mTBI" if any abnormality is apparent on CT scans [164]. (This concept is also used by the authors of this chapter because it implies that head

Table 1 Definition of mild TBI according to the 2009 VA/DOD guideline

Criteria	Mild
Structural imaging	Normal
Loss of consciousness (LOC)	0–30 min
Alteration of consciousness/mental state (AOC)[a]	A moment up to 24 h
Posttraumatic amnesia (PTA)	0–1 day
Glasgow Coma Scale (best available score in first 24 h)	13–15

[a]AOC has to follow immediately the injury. Typical symptoms would be looking and feeling hazy, confusion, memory disturbances (difficulties in thinking clearly, responding to questions, description of the events before and after the trauma)

injuries leading to mild symptoms may be accompanied by both normal and positive CT scans, and the latter may require distinct care.)

The origin and cause of mild TBI are not much different than that of moderate or severe cases as road traffic accidents and falls dominate the field followed by assaults and sports-/recreation-related injuries [78].

Sports-related chronic repetitive head trauma is considered as a subgroup of mTBI. Head injury is a hazard of many sports – especially combative sports such as boxing, kickboxing, soccer, ice hockey, football, and many others [37]. Concussion during sport activity is common. Concussion is a clinical syndrome with transient impairment of consciousness or disturbance of equilibrium or vision. It may be followed by post-concussion syndrome including headache, anxiety, and cognitive and psychosocial problems. Compared to the other causes of mTBI such as road traffic accidents and fall, the mechanism of sports-related head trauma is slightly different, and the intensity is lower and frequently referred to as chronic repetitive mTBI.

Pathobiology of Mild TBI

mTBI is predominantly evoked by acceleration-deceleration type of head injury, and in a majority of cases, no direct impact to the head is involved. Wide diversity of evoking forces as well as the subtle nature of structural damage makes it extremely difficult to establish relevant animal models and to understand the pathobiology. Most recent studies highlight the importance of electrolyte alterations in line with metabolic uncoupling as well as microscopic structural alterations most probably reflected in diffuse neuronal and axonal injury [69, 121, 122].

Injury Severity and Triage

As far as the severity of TBI is considered, most classifications rely on the Glasgow Coma Scale. While this approach might be well justified in severe TBI, in less severe forms, particularly mild TBI, several data indicate that a single line between GCS 12 and 13 can hardly separate moderate and mild TBI: in the case of GCS 13, the outcome is primarily defined by the neuro-worsening, seizures, and medical

Table 2 Conditions ("red flags") indicating intracranial hemorrhage in cases of complicated mild TBI

1. LOC
2. Progressive headache
3. Alcohol/drug intoxication
4. Seizure
5. Unreliable history
6. Age under 2 years
7. Repeated vomiting
8. Amnesia
9. Physical signs of skull fracture
10. Repeated trauma
11. Severe maxillofacial trauma
12. Child abuse
13. Significant subgaleal swelling/collection
14. Coagulopathy/altered hemostasis
15. Diabetes
16. Age over 60

complications score (just like in the case of GCS 12 and 11 that are more severe forms of TBI), while in the case of GCS14 the intracranial pathology revealed by imaging will herald the outcome [30].

To this end, other factors such as loss of consciousness, posttraumatic amnesia, and their duration might help. As it has been alluded to before, most classifications require a negative CT for mild TBI; nevertheless, most recent studies identified a novel patient category that is the CT-negative, MRI-positive patient population who definitely should fall into a subgroup requiring special attention and further understanding.

Whatever classification is applied, none of them can thoroughly answer the two major questions associated with mild TBI that are: what is the actual chance for an intracranial complication in the acute setting and whether there is a possibility of late transient or permanent deficit.

Two modalities that may help in this matter are the imaging and the biological markers associated with any purported intracranial pathology (see later).

For the acute setting, the most important issue caretakers have to elucidate is the existence of an intracranial injury that may require further attention. While the majority of mild TBI cases show up at the outpatient department/emergency room without any indication of an intracranial complication, there are some conditions ("red flags") where special cautiousness should be exercised (Table 2) [4, 142].

Unfortunately, it is rather hard to provide a clear guideline for the triage and subsequent decisions to make; nevertheless, two strategies can clearly be detected and followed: the first is close observation on the floor for 12–24 h, and the second is CT scanning of all suspicious cases (Fig. 1).

While cost-efficiency reports clearly support the latter strategy, negative effects of cumulative radiation over time is a major precaution. It is also obvious that not every subject can be handled the same way, as in case of young women and children observation should have priority and even if imaging is becoming necessary MRI is the primary modality to choose.

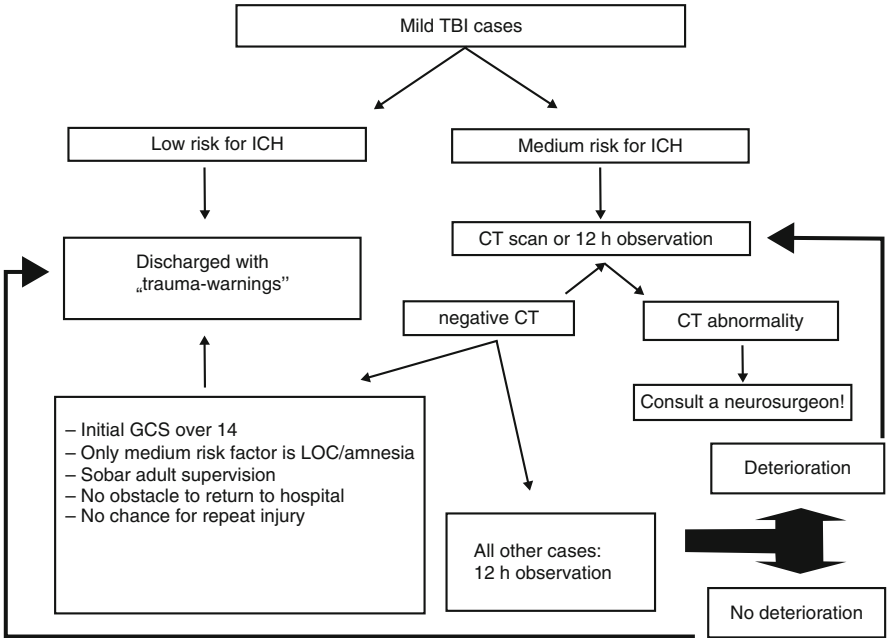

Fig. 1 Diagnostic algorithm of mTBI cases regarding risk of ICH

Unfortunately routine application of cognitive tests is not common, and just like imaging, cognitive tests did not prove sufficient to predict late complications either (*see also sports-related injuries*).

Although in mTBI the probability of associated extracranial injuries is less common, there is a significant chance for C-spine injury; thereby, precautions (in-line immobilization, C-collar) should be taken until the spine is cleared diagnostically. To exclude such injuries in a timely fashion, analysis of injury mechanisms (e.g., fall to the face) and the patients' complaints (neck pain, numbness) may provide invaluable information.

The Role of the Neurosurgeon

Besides evacuation of intracranial bleedings complicating originally mild TBI cases, the most important task a neurosurgeon should undertake if involved in the triage or care is the identification of "red flags." Of these, the most important is the exclusion of any factor that may be associated with altered hemostasis (Table 2). This issue has gained particular importance recently as in the aging population that represents a growing percentage of TBI cases cerebrovascular conditions frequently require the application of hemostatic treatment strategies including the K-vitamin antagonist warfarin/coumarin and drugs inhibiting platelet-aggregation such as aspirin or clopidogrel [106, 110].

When hemostasis is a problem, it is particularly important to analyze the time between injury and the first CT scan, and if any suspicion exists about a negative CT scan, it should be repeated as such second CT often times reveals the appearance of an intracranial lesion.

To this end, the role of hemoglobin-sensitive MR sequences such as hemogradient imaging or susceptibility-weighted imaging is not clarified yet although cost-efficiency issues may definitely hinder their applications (Fig. 3).

Measures to normalize altered hemostasis require individual decision with balancing between the chances for intracranial complications and their potential evolutions and cerebrovascular consequences of physiological coagulation.

It is of note that INR over the therapeutic range requires prompt intervention that can be easily executed as current evidence supports that a temporary suspension of these medications is not necessarily associated with substantially increased risk of cerebrovascular complications [124].

In case of altered hemostasis if the first CT had been performed within 4 h of injury, a considerable chance of a late-appearing ICH still exists – thereby close observation and in case of any deterioration repeat scanning are suggested.

As it has been alluded to before, contemporary knowledge is insufficient to predict the occurrence of mid- or long-term complications of mTBI, particularly, as the definition of these conditions such as that of the "post-concussive syndrome" is not well delineated [81, 119].

Imaging of Mild Traumatic Brain Injury

Detection and description of the specific pathology underlying mTBI would require the development of novel diagnostic tools. These tools should be capable of (1) evaluating actual injury severity within the wide spectrum in mTBI based on objective parameters, (2) assessing prognosis, (3) avoiding "overlooked" cases, and (4) improving management of special cases as sport or combat-related trauma. The pathophysiology of mTBI is likely to involve numerous different mechanisms; however, diffuse axonal injury (DAI) is thought to play a central role, based on a large number of both human and animal investigations [120]. Although the research on mechanisms following mTBI and especially their correlation to clinical features still raises many questions, a wide range of advanced imaging methods are emerging with a promise of detecting different aspects of the traumatic sequelae.

Microstructural pathology as axonal deformation and swelling causes change in water micro-compartments and so in diffusion parameters, which can be detected by diffusion weighted and diffusion tensor imaging (DWI, DTI). Focal microscopic bleeds that may develop as part of DAI are most successfully detectable by susceptibility-weighted imaging (SWI), a method exploiting the magnetic property of iron. High-resolution, three-dimensional T1-weighted images allow precise volumetric analyses to be performed that are able to shed light on subtle changes in the brain macrostructure, due to edema and atrophy following injury. Beyond the

advanced investigation of brain structure, MR spectroscopy (MRS) offers information of the metabolic state of the brain, by measuring specific magnetic signal from mainly 1H nuclei in different metabolites. Getting to higher level, the effect of injury on brain functions as perception or also cognitive tasks (as typically affected memory functions) is possible to be investigated by functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT).

Well-developed, computerized analytic methods are available to gain objective, robust, statistically relevant, and often quantitative results from most imaging modalities.

Overall, recent imaging methods provide an all-around approach to understand mTBI; as a result, several valuable "markers" have been proposed for mTBI.

However, to date the findings remain heterogeneous, and further research is needed to provide a standardized, clinically available diagnostic process.

Conventional Imaging

Computed Tomography (CT)

Computed tomography is the gold standard to examine patients with mTBI if imaging is necessary [32]. Plain cranial X-ray films were totally abandoned due to their inability to detect intracranial pathologies. X-ray gives a false feeling of confidence during the triage process while neither its' resolution or the scope of the modality justifies this. The advantage of CT scanning is that it is readily available in every trauma center, and even agitated patients can be examined due to the short acquisition time. It provides voxelwise X-ray attenuation maps with good spatial resolution, and acute hematomas can be easily visualized due to their high degree of X-ray attenuation.

The disadvantage of the technique is that it applies ionization radiation thus it may add a risk to cancer development – a problem significantly reduced in novel low radiation instruments. Other disadvantage is that diffuse white matter lesions may remain hidden on the images.

The main purpose of CT scanning is the identification of those patients who need hospitalization and further observation. It should be noted that only a minority of patients (<10 %) with inclusion criteria for mTBI will have positive CT scan [40, 55, 145]. Overwhelming majority of classifications (*vide supra*) then declare these patients as complicated or moderate TBI cases.

Several guidelines (e.g., [61, 63]) have been put forward to determine the circumstances when CT scanning is required. The common points for indication of a CT in patients with mTBI are the following: loss of consciousness, vomiting, amnesia, suspected cranial fracture (basal, open, or depressed), neurological deficit, coagulopathy, post traumatic seizure, age>60 years, and high energy injury (i.e., fall from height, motor vehicle accident, etc.) (also see Table 2).

By several definitions, traumatic brain injury is considered "mild" when the CT is negative (*vide supra*). Thereby in this chapter, we allude to the use of CT in cases of suspected mTBI.

In suspected mTBI, CT may visualize small macroscopic hemorrhages such as cerebral contusions, traumatic subarachnoidal hemorrhages, and extra- or subdural hematomas. Nevertheless, small hematomas in patients with mTBI may remain hidden due partial volume effect (mostly on the bone-brain interface) on the temporal and frontal skull bases. Such hemorrhages in mTBI appear to progress within the first 2 h after injury and reach their final volume within 24 h [58]. It is of note that pathology on acute CT in mTBI may not predict the outcome 3 months after injury [82], and clinical variables together with age may be stronger predictors for long-term outcome [62].

The above-listed limitations of CT in terms of resolution and/or outcome prediction ignited the search for advanced neuroimaging modalities.

Conventional MRI

Conventional MRI (T1- and T2-weighted, fluid attenuation recovery, FLAIR) is more sensitive to focal injuries than CT; higher number and volume of lesions are detectable [67]. However, in many cases of mTBI, conventional MRI also fails to detect the diffuse and subtle damage, and the clinical interpretation of detected lesions is debatable [59].

Although CT remains the gold standard imaging modality for TBI, MRI is suggested to be performed in children and young women due to the absence of ionizing radiation. Unfortunately MRI has some contraindications to be kept in mind, as a patient with pacemaker, claustrophobia (open magnet can be an alternative), metallic foreign body, etc.

Advanced MRI Techniques

Diffusion Tensor Imaging (DTI)

DTI measures Brownian movement of water molecules and applies at least six diffusion gradient directions, thus is able to provide information on the extent and directionality of diffusion. Fractional anisotropy (FA) refers to the degree of directionality, calculated from the variation in the eigenvalues of the diffusion tensor, while mean diffusivity (MD) or the synonym apparent diffusion coefficient (ADC) refers to the overall, rotationally indifferent mobility of water molecules [7]. The character of diffusivity in brain is widely accepted to be associated with fiber tracts, i.e., axons and myelin sheath. Thus, FA and MD are theoretically able to detect DAI, an effect of shear-strain deformation of the fiber structure, regarded to lie behind mTBI. Furthermore, the sensitivity to changes of water micro-compartments

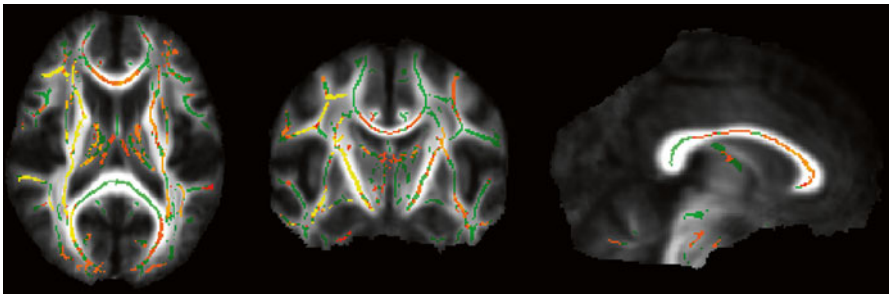

Fig. 2 This voxelwise analysis (Tract-Based Spatial Statistics, FSL – FMRIB's Software Library) compares an mTBI group's acute data and a matched control group ($n = 14$ in both groups, respectively). The red-yellow voxels represent significantly (corrected $p < 0.05$) decreased fractional anisotropy (FA) in the mTBI group compared to the control group. Significant voxels (*yellow-red*) are overlaid on the group mean white matter "skeleton" (*green*) and the group mean FA image (*grayscale*). Images are shown in radiological convention (right = subject's left)

makes DTI able to assess different subtypes of edema and other important components of the traumatic tissue [10].

A large cohort of studies investigated diffusion in mTBI focusing on several different relations, e.g., with age, acute or chronic phase, clinical symptoms or neuropsychology tests, recovery, and sports- and combat-related injuries.

Many investigations on mTBI found reduced FA or elevated MD (ADC) in mildly injured patients (Fig. 2) and often interpreted the findings as reduced integrity, i.e., misalignment of axonal and myelin structures due to shear-strain forces, including local expansion of axonal cylinder or axonal disconnection [3]. On the other hand, other studies observed elevated FA or reduced MD acutely after mild injury along several white matter regions [94]. One possible underlying mechanism is cytotoxic edema, as in this condition the injury induced altered function of gated ion channels results in intracellular swelling and decrease in extracellular water that causes reduced radial diffusivity. The output yielded by DTI may show a summarized effect of the two basic mechanisms, microstructural disintegration and cytotoxic edema. A recent study also found bidirectional irregularities in DTI parameters after injury [86]. The actual dominance of these substantial mechanisms in the white matter may theoretically depend on temporal, spatial factors, attributes of the patient, and the circumstances of injury. Future research should shed light on the proper interpretation of the different diffusion indices possibly by focusing also on less robust parameters such as eigenvectors and eigenvalues.

Findings of follow-up studies are also various; some longitudinal studies revealed partial normalization of DTI indices after different periods, while other investigations indicated traumatic microstructural alteration to be more stable or even to evolve. There are promising observations of the relation of DTI findings with cognitive or psychological dysfunction and clinical outcome, especially in moderate to severe cases [109].

An advanced analysis of DTI data, DTI tractography, was recently shown to be competent in assessing mTBI and outcome prediction.

Diffusion spectrum imaging (DSI) that is thought to resolve crossing fibers (unlike conventional DTI) recently provided novel insights of the human white matter microstructure [161]. This altogether with novel connectomic techniques may revolutionize understanding microstructure alteration in mTBI.

Volumetric Analysis

Due to the high resolution and contrast of T1-weighted images, especially the three-dimensional T1 images (e.g., MPRAGE), it is possible to closely estimate volumes of specific brain structures. First, this was achieved by manual measurements, which were later replaced by automatic segmentation algorithms, voxel-based morphometry techniques, and other computer-based methods offering the estimation of both global and regional brain volumes.

Different manifestations of brain atrophy following injury were identified in a large number of morphometric studies conducted on mixed (mainly moderate to severe) TBI populations [163]; injury severity or cognitive function was correlated with atrophy rate; in one group outcome was found to be independent from atrophy; the association of post- traumatic stress disorder with atrophy of whole brain, corpus callosum, anterior cingulum, and hippocampus was presented by some studies.

However, a low number of studies investigated homogenous mTBI groups. MacKenzie et al. found global atrophy developing in 3 months in a group of mild and moderate injured patients that was correlated with LOC [91]. Specific gray matter volume decrease was also shown, but was not predictive for outcome. A recent follow-up study raised the possibility of post-injury edema formation in mTBI that is detectable by volumetric analysis [157].

Susceptibility-Weighted Imaging (SWI)

SWI is particularly sensitive in detecting both intravascular venous deoxygenated blood and extravascular blood products [52].

It was shown to be the most sensitive modality in detecting microhemorrhage, primarily in pediatric TBI of mixed severity [155]. The correlation of SWI lesion number, volume, and location with neuropsychological functioning or with outcome was also presented in children.

In contrast, adult data and especially studies of mTBI are limited. A study proved the superiority of SWI over CT and conventional MRI in sensitivity to microhemorrhage in a group of adults with dominantly severe TBI patients [1].

Microhemorrhages do not seem to be frequent in mTBI. Based on data from amateur and professional boxers and on experiences of SWI using diagnostic centers, SWI lesions in mTBI occur in about one out of ten patients. This lesion occurrence is comparable to the lesion occurrence (not only microhemorrhages) detectable with conventional imaging methods. Future research should reveal the relation between injury circumstances, conventional imaging, SWI, and outcome, also providing data on the overall clinical importance of SWI in lesion detection in mTBI (Fig. 3).

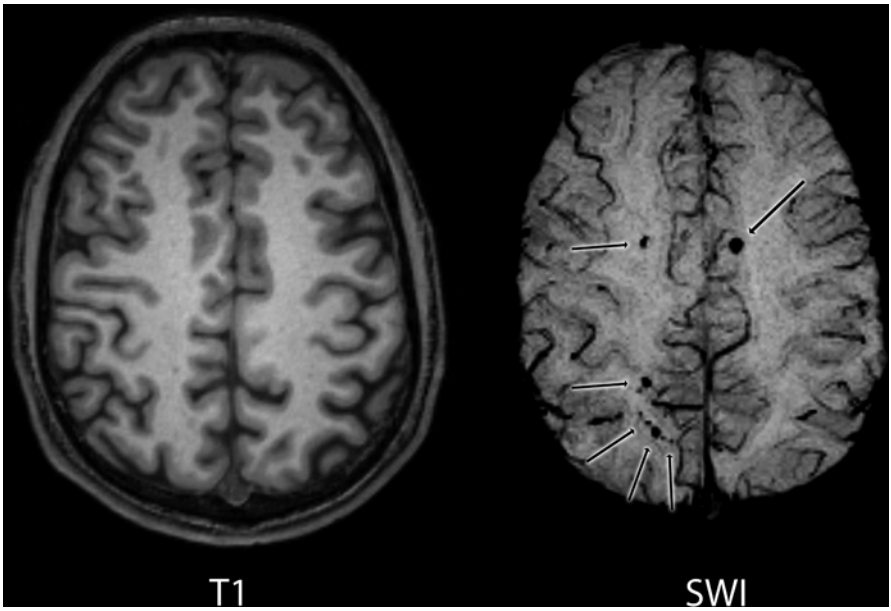

Fig. 3 T1-weighted and SWI images of a mTBI patient (GCS = 14, LOC = 3 min. PTA = 2 h) acquired 20 h after injury. SWI revealed several microbleeds (*black arrows*). These lesions are scarcely, or not detectable on the T1 image. CT image was diagnosed without trauma-related pathology

Magnetic Resonance Spectroscopy (MRS)

By measuring solute-specific magnetic signals from 1H nuclei, MRS offers in vivo chemical information of the brain tissue. This method can be used to detect the potentially altered metabolism following mTBI.

The main peaks of a proton MRS spectrum refer to the following metabolites: N-acetylaspartate, marker of neuronal integrity; choline which may be altered in inflammation, proliferation, or membrane damage; myo-inositol, which is a glial marker; lactate, that is elevated in ischemic/hypoxic conditions; creatine and phosphocreatine, which are related to energy metabolism but are often assumed to be relatively constant, so are widely used to standardize other metabolites; and glutamate and glutamine (glx when combined) which are important neurotransmitters or metabolites.

First MRS studies on mTBI patients showed various irregularities in metabolites: decreases of N-acetylaspartate (NAA) were found in the corpus callosum and parietal white matter [49]; another study found normal NAA levels but increased choline levels in the frontal lobe [44]; a finding also described in the occipital lobe [49]. A 2-month follow-up investigation presented recovery in NAA in pericontusional tissue.

However, correlation of metabolite irregularities and clinical features were not presented convincingly, only in severe TBI patients. The instability of creatinine

levels in mTBI was suggested to be a confound factor as creatinine was suggested to change in hypo- or hypermetabolic state or different diseases.

Later studies conducted on more homogenous mTBI groups with better-defined acquisition time points supported different metabolites (mainly NAA and choline) to be associated with outcome [159].

Interestingly, relation between NAA reduction at certain white matter regions and posttraumatic headache was also postulated.

To conclude, MRS has a great potential in elucidating the effects of mild injuries on the brain. By taking acquisition circumstances to common denominator and revealing the specificity of the different metabolic alterations, MRS may become a helpful diagnostic and prognostic tool.

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI detects local hemodynamic changes following increased metabolic rate in neural activity, by measuring the blood oxygen level dependent (BOLD) contrast.

Specific cognitive, motor, and memory tasks or sensory stimulation is repeated, and the associated BOLD signals are compared. Functional connectivity investigation reveals brain areas with correlated fluctuations (i.e., coupled functionality) during an experimental task or resting state (in the absence of any active task or external stimulus).

There is a growing body of evidence that fMRI is able to detect altered patterns of brain activation following mTBI [64].

Most studies concentrated on memory functions, especially working memory, given that cognitive impairment is a major concern in mTBI. The altered activation that is primarily detected in the dorsolateral prefrontal cortex was suggested to underlie working memory dysfunctions. A few studies focused on spatial working memory or declarative memory. Non-memory function was also tested, for instance, by a motor-sequencing task.

In these studies, various injury-related changes of BOLD signal level and distribution were detected. Some studies also found attenuated activation in mTBI patients (Fig. 4) that may be a result of injured neural network. Others reported increased or additional activation. These findings may be explained as results of neural reorganization or functional accommodation [64].

Correlation between BOLD signal change and neuropsychological findings or task performance was proposed; however, the alteration of BOLD signal distribution was observed independent of clinical signs as well. A relatively low number of longitudinal studies suggested that the cessation of symptoms over time is associated with the normalization of cortical patterns.

The recent wave of resting state fMRI studies on mTBI patients provided further important insights to the functionality of the injured brain. Depending on explored areas, both decreased and increased connectivity was registered. Alterations in the default mode network connectivity are suggested to have clinical connotation [68].

Integration of structural and functional connectivity data may be a subsequent step to understand the background of mTBI related complaints [135].

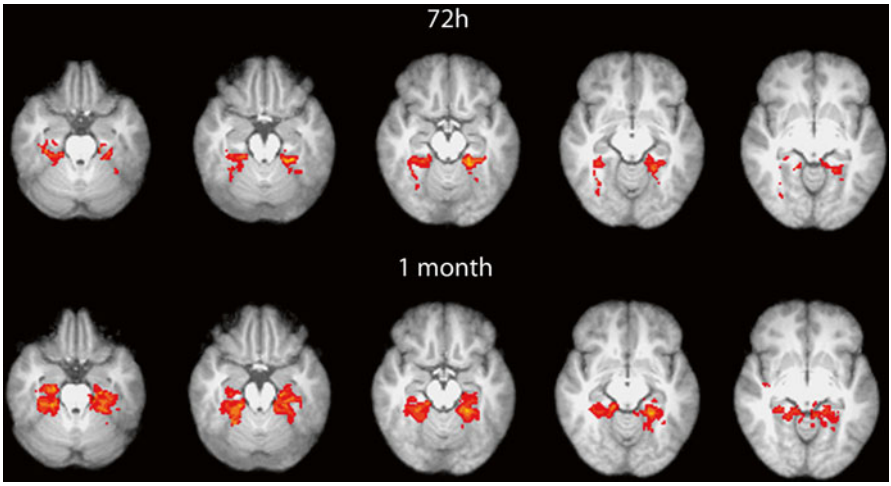

Fig. 4 Decreased level and extent of activation was detected during spatio-visual memory task (Roland's Hometown walking) in parahippocampal regions by fMRI at 72 h compared to 1 month after injury within a group of mTBI patients. The red-yellow voxels show the significant group activations (10 patients, same Z score threshold) that are overlaid on MNI 152 standard brain slices. This activation difference was validated by statistical analysis as well (paired *t*-test)

Nuclear Imaging: Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT)

PET

PET imaging is a robust method to reveal regional glucose metabolism of the human brain, generally using isotopes as [^{18}F] fluorodeoxyglucose (FDG). However, it has been less widely used as fMRI because of its lower availability, spatial-temporal resolution, and ionizing radiation, especially in the investigation of the healthy brain.

In severe TBI, a triphasic metabolic pattern was demonstrated both in humans and animal models, which involved an acute hyperglycolysis followed by a prolonged period of metabolic depression and a final recovery [12]. Data in mTBI are limited and inconsistent. Studies agree that metabolic irregularities may persist for months or even years after injury, but both hypo- and hypermetabolism were detected along different brain areas [26].

SPECT

Other possible way of assessing brain metabolism is the measuring of blood flow by SPECT. This method is more accessible and cheaper than PET; thus, broader range of information was obtained in mTBI.

Studies that focused on the acute phase of mTBI revealed hypoperfusion in various brain regions including the frontal lobes [5]. The incremental validity of SPECT beyond CT was also established; however, quantitative correlations to clinical aspects were not supported. Patients with persistent posttraumatic complaints also show hypoperfusion, often in the frontal and temporal lobes. Although the clinical significance of SPECT irregularities is not clear yet, this method was proven to be highly sensitive to mTBI; thus, a normal post-injury SPECT scan may potentially exclude unfavorable outcome [50].

Biomarkers of Mild Traumatic Brain Injury

Despite a substantial improvement in this area, mild TBIs, compared to moderate and severe brain injuries, remain often challenging to diagnose, mostly due to rapid resolution of acute signs and symptoms and the absence of objective evidence of injury on neuroimaging.

Furthermore, Ruff and colleagues [128] conducted an accurate analysis on potential confounders in the current diagnostic schemes for TBI and highlighted the difficulty in differentiating mild TBI from non-TBI pathologies that may present with similar symptomatology. Such distinction is particularly relevant in light of the high reported incidence of mild blast TBI in military personnel returning from combat [85].

The recognition of the impact of previously undiagnosed TBI further pointed out the urgent need for accurate and objective diagnostic criteria that can be represented by the clinical use of biomarkers. Indeed, a consensus definition of TBI [100] recognized that advanced imaging and other novel biomarkers might allow better characterization of TBI in individuals, advancing care to personalized management. This could be a pragmatic solution to the problem of diagnosis and categorization allowing establishment of effective clinical protocols and pathways for clinical care.

Importantly, although most patients with minor head injury can be discharged without sequelae after in-hospital observation, a small proportion of patients have intracranial injuries (ICI) and require neurosurgical intervention [55]. Early diagnosis of ICI by computed tomography (CT) followed by early surgery is very important in the treatment of such patients. Although, several rules have been published aimed at identifying patients with higher risks for CT findings and/or neurosurgical intervention, the use of CT for minor head injury has become increasingly common due to several causes. A large proportion of mTBI patients, between 30 and 50 %, are intoxicated [114], which confound several of the clinical predictors included in the decision rules. In addition, approximately 10 % of physicians reported that New Orleans Criteria guidelines and Canadian CT Head Rule were uncomfortable to apply, and the guidelines have been shown to be misinterpreted by approximately 5 % of physicians [144].

More selective use of CT scans for investigation of patients with minor head injury could lead to large reductions exposure to potentially harmful ionizing

radiation [138] as well as health-care costs. The challenges of early diagnosis and identification of disease-modifying drugs have created a need for biomarkers that reflect core elements of the disease process. The possibility of using new biomarkers in patients with mTBI could provide a rapid, definitive, and cost-effective diagnostic test for brain injury that prove invaluable in diagnosis and improve management of brain-injured patients reducing significantly CT usage.

Several studies from different research groups have explored the ability of different biomarkers to aid in decision making in the management of patients with mild TBI. These efforts initially concentrated on S100, but lately new biomarkers have been explored.

Here, we review the candidate serum biomarkers for mTBI. We focus on established biomarkers (biomarkers evaluated in several studies by various research groups) as well as novel promising markers, discussing their potential roles as TBI diagnostic tools and providing a practical guide to their implementation in the clinic.

Biochemical Markers of Brain Damage for mTBI

A biomarker is an objective measure of a specific biological or pathological process that can be measured in body fluids such as cerebral spinal fluid (CSF) and blood. Specifically, traumatic injury to the brain causes cellular damage and disintegration, leading to release of cell type-specific proteins such as S100B, glial fibrillary astrocytic protein (GFAP), and ubiquitin C-terminal hydrolase (UCH-L1) into biofluids (CSF and blood). As a result, biomarker concentrations accurately reflect cerebral pathological changes and are directly proportional to the magnitude of the injury.

The blood, easily and routinely accessible following mild TBI, is the optimal source of biomarkers, and the presence and quantity of the biomarker can be accurately determined by sensitive enzyme-linked immunosorbent assays (ELISAs).

Specific brain injury biomarkers can have utility as blood-based TBI diagnostic and monitoring tools. The use of biomarkers would be of particular value in identifying mTBI patients with ambiguous neurological symptoms or intoxicated or when neuroimaging cannot be obtained or is non-diagnostic. In addition, biomarkers for TBI could have important prognostic functions. Accurate identification of patients who sustain mild TBIs will facilitate development of guidelines for return to work or sports activities and also provide opportunities for a better management and pathways for clinical care.

S100B

The S100B is a calcium-binding protein mainly expressed in astrocytes but also present in other nervous cell types such as microglia and neurons and extracerebral cells such as adipocytes, chondrocytes, and bone marrow cells [36]. A number of studies have shown that levels of protein S100B in biological fluids correlate with

the presence and severity of neurological disorders. In 1995, Ingebrigtsen et al. [60] reported, for the first time, the use of serum S100B in patients with mild TBI. They found that S100 levels were associated with the development of symptoms in 67 % of patients with negative CT after minor head injury. Since this original study, several studies from different research groups have explored the ability of this biomarker to aid in medical decision making in the management of patients with mTBI. Although few researches tried to assess the relationships between S100 levels and short- and long-term symptoms with contrasting results [61, 130], significant efforts have been concentrated on the diagnostic accuracy of S100B for intracranial injury evident by CT. Consistently, S100B demonstrated high sensitivity (75–100 %) for CT-evident injury [158] but low specificity due to the extracerebral sources of the protein [126].

Recently, Unden and colleagues [158] conducted a meta-analysis involving 2,466 adult mTBI patients with the aim of evaluating whether S100B can predict normal CT findings after minor head injury. They concluded that low serum S100B levels (<0.10 μg/L) taken within 3 h of injury predict normal CT findings after mTBI in adults with negative predictive values of 90–100 % [158].

Despite these very promising results, as mentioned above, a significant limitation to the use of S100B as a potential screening agent for brain injury is the lack of specificity in the setting of trauma patients [126]. Nevertheless, the inclusion of S100B in a panel of brain biomarkers can improve sensitivity and the predictive value of the initial CT scan.

Finally, S100B is not a useful marker in children less than 2 years of age due to high normative values in that age group [17, 118].

Evidence for Novel Candidate Biomarkers in Mild TBI

S100B is the most commonly studied and more frequently used biomarker. However, the lack of specificity for the brain has been limiting its application as diagnostic tool in brain injury. As a result, other more specific biomarkers have been investigated to obtain a clinically useful specificity and positive predictive value (PPV) for brain injury after mild TBI. These candidate biomarkers include glial fibrillary acidic protein, neuron-specific enolase, and ubiquitin C-terminal hydrolase. Of these, glial fibrillary acidic protein and UCH-L1 seem most promising because of the clinical specificity.

The following sections review our current knowledge on these novel protein biomarkers with respect to their diagnostic and prognostic ability in mild head injury. However, these markers have not been sufficiently investigated in mTBI, and further studies are needed before any conclusions can be drawn.

Neuron-Specific Enolase

Neuron-specific enolase (NSE) is a glycolytic pathway enzyme, localized predominantly in neuronal cytoplasm. This protein, originally identified in neurons, was successively found in other cell types including erythrocytes, platelets neuroendocrine cells, and oligodendrocytes.

Several studies demonstrated that NSE is a sensitive indicator of neuronal cell death and serum levels increase after TBI and correlate with the severity of the injury [125, 165]. To date, there are still little data on the utility of serum NSE measurements in mild head-injured patients. However, NSE concentrations have been shown to be higher in patients with mild TBI compared to control [35]; there was no convincing evidence of ability of this marker to function as a stand-alone predictor of post-concussion syndrome (PCS) [35].

In a recent study of 141 patients with mTBI evaluating the predictive value with respect to the short- and long-term neuropsychological outcome, NSE concentrations within 4 h after injury alone had a limited discriminative power [156]. Conversely, NSE in conjunction with other clinical and demographic variables demonstrated high accuracy (c-statistic 0.895) in predicting poor outcome at 6 weeks post-injury [156].

To note, false-positive values have been reported in the setting of combined CNS injury and shock [116] or hemolysis [117]. Furthermore, increased NSE is also found in types of tumors such as small cell lung cancer, neuroblastoma, and seminoma.

Glial Fibrillary Acidic Protein

Glial fibrillary acidic protein (GFAP) is a monomeric intermediate filament protein that represents the major component of the astroglial cytoskeleton [39]. It is found in glial cells in gray and white brain matter [103] and is highly specific marker for CNS pathology as is not found outside the central nervous system.

In studies concerning severe TBI, the relation between injury severity and serum GFAP has been investigated and assessed. Levels of GFAP are related to the severity of brain injury and outcome [105, 160].

Recently, two concurrent studies examined the value of serum GFAP as a marker of brain injury in patients with mild TBI [101, 112]. In 108 patients with mild and moderate head injury (GCS scores of 9–15), the accuracy for intracranial injury evident by CT scan was 0.79, with a sensitivity of 97 %, a specificity level of 18 %, and the negative predictive value of 94 % using cutoff level of 0.035 ng/mL. Further more, with a GFAP cutoff value of 0.17 ng/mL, the patients requiring neurosurgical intervention findings were identified with a sensitivity level of 100 % and a specificity level of 42 % and negative predictive value of 100 % [112]. Accordingly, in their study including 94 patients with mild brain injury (GCS between 13 and 15), Metting et al. [101] reported higher GFAP levels within 3 h after injury in patients with an abnormal admission CT compared to patients with a normal CT. GFAP showed a high negative predictive value for MRI 3 months post-injury (0.82) indicating that low GFAP levels in serum predict a normal MRI. When compared to S100B, GFAP appears a more sensitive marker. GFAP was found to be related to imaging and outcome as defined by return to work, whereas S100B was found not to be of prognostic value in this patient category. However, the authors conclude that as the category of mild TBI includes less severe injuries with no detectable GFAP (63 % in their study), the predictive value of GFAP appears limited and not useful in making clinical decisions or for prediction of outcome in this patient group [101].

Ubiquitin C-Terminal Hydrolase

Ubiquitin C-terminal hydrolase (UCH-L1) is a highly abundant neuron-specific enzyme, representing between 1 and 5 % of total soluble brain protein [84]. It has been suggested that UCH-L1 plays an important role in the removal of excessive, oxidized, or misfolded proteins during both normal and neuropathological conditions including neurodegenerative disorders [75]. This protein is released into the extracellular space as a consequence of cell destruction under pathological conditions. Measurable amounts of this damage marker are present in cerebrospinal fluid (CSF) and blood and are directly proportional to the magnitude of the injury. Because of these characteristics and its high brain specificity and abundance in the CNS, UCH-L1 has been proposed as a novel biomarker for TBI. Previous experimental and clinical studies have shown significantly increased UCH-L1 levels in CSF and in serum in severe TBI patients compared to uninjured subjects. Also an association between UCH-L1 concentrations and injury severity and clinical outcome was observed [104].

A study has been conducted recently investigating UCH-L1 in 96 adults with mild and moderate TBI (GCS score 9–15) [113]. Mean serum UCH-L1 levels were significantly higher in patients with CT positive (1.618 ng/ml) compared to patients with CT negative (0.620 ng/ml). Using a cutoff level of 0.09 ng/mL, the sensitivity and specificity of UCH-L1 for detecting intracranial lesions on CT were 100 % and 21 %, respectively, and a negative predictive value of 100 %. In addition, a correlation between UCH-L1 concentrations and measures of injury severity including the GCS score and neurosurgical intervention was observed.

Evidence for Biomarker Use in Children with Mild Head Injury

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in infants and children and remains a public health problem of enormous magnitude. Case series from multiple trauma centers report that 75–97 % of trauma deaths in children result from head injuries [154]. The incidence of TBI is calculated as 1/285 in babies younger than 1 year [65], and up to 80 % of deaths in children younger than 2 years are due to inflicted TBI – often referred to as shaken baby syndrome [14, 77].

Patients with severe TBI are easy to recognize in clinical practice, but the correct diagnosis of mild TBI (mTBI) in babies and younger children is difficult even for experienced physicians, partly because questioning rarely provides a good history of trauma and partly because infants present common nonspecific clinical symptoms [21] with an unremarkable physical examination [54, 107].

Despite algorithms for the evaluation and triage of children and adolescents with mTBI are available [79] to reduce unnecessary CT scan and inpatient observation, most CT and short hospitalization can still be potentially avoided, because 93 % of children with mTBI have no intracerebral lesions [57].

Several reports suggested that biomarkers might be valuable in pediatric TBI [15, 77], and there is a clear trend toward increased international efforts to evaluate the use of biomarkers in pediatric TBI [23, 77].

However, while the adult literature related to biomarkers in TBI and outcome prediction is extensive, the pediatric literature is still limited, especially for mTBI. In addition, the biomarkers which are best studied in adults have pediatric-specific limitations; NSE is affected by hemolysis, a particularly important problem in infants and young children [13], while S100B has high normative concentrations in young children [19].

In a study evaluating 100 patients after iTBI and nTBI, the sensitivity and specificity of the initial NSE for identifying TBI were 71 and 64 %, respectively [14]. Serial serum sampling of NSE in children ($n=152$) with mild (61 %) and severe (30 %) TBI shows that higher concentrations are associated with worse outcome. The initial and peak NSE concentrations showed a stronger correlation with outcome in children less than 4 years than those >4 years of age [16].

The role of the S100B marker in the initial assessment of children with mTBI is still controversial, and not really defined [42]. Berger and colleagues report [17] that, in children under 1 year of age arriving at the emergency department with nonspecific symptoms but with suspicion of TBI, S100B was neither sensitive nor specific for iTBI, and an increased level was measured in 90 % of patients with non-brain injury. However, the same group showed in a later study that the mean concentrations of S100B were significantly greater than normal control concentrations in children with mild and severe TBI ($n=152$), and there was a significant correlation between outcome and serum marker in children both over and under 4 years [16]. Bechtel et al. [11] reported a study with S100B levels in serum after closed head injury in children. They found a PPV for intracranial injury of only 20 % but a high negative predictive value of 90 % at the same cutoff. They also investigated the impact of bone fractures on S100B levels and found that these extracranial injuries may be responsible for the poor specificity of S100B in trauma. In a study of 109 children, Castellani et al. [23] showed that S100B gives a sensitivity of 100 % and reduces unnecessary cranial CT scans. Hallen et al., who did a study on 111 children, suggested that S100B could be a valuable diagnostic tool added to those used in clinical practice today [53]. Recently, Bouvier et al. [21] evaluated the utility of serum S100B measurement in mTBI management on a large cohort ($n=446$) of children with closed head trauma divided into three groups on the basis of TBI severity (minimal, mild, and severe). Levels of S100B in serum correlated with severity of injury. In addition, measurement of S100B accurately identified patients with CT positive (100 % sensitivity and 33 % specificity) and children with poor clinical evolution (100 % sensitivity and 36 % specificity), demonstrating a potential clinical utility of S100B for the management and outcome prediction of children with mTBI.

Recently, two novel candidate biomarkers, UCH-L1 and αII-spectrin breakdown product 145 kDa (SBDP145), have been evaluated by Berger and colleagues [18] in children with TBI and healthy controls. Serum UCH-L1 and SBDP145 concentrations were significantly greater in TBI patients than in controls, but the increase was exclusively seen in subjects with moderate and severe TBI, no after mild TBI. Both

markers were correlated with glasgow outcome scale (GOS), and this correlation was stronger than the correlations with NSE, S100B, or MBP [18]. These encouraging results support and highlighted the need for further studies with more inclusion.

Venous cannulation is not always performed in children with mTBI, especially in asymptomatic subjects. Urine or capillary measurements of biomarkers would be a suitable option because this sampling method is less invasive and can be easily used for children in the emergency department. Nevertheless, separate reference and injury values must be studied before this method can be considered [158].

Taken all together, these data suggest that after validation in a multicenter study that includes a high number of cases, biomarker determination might be an invaluable diagnostic tool that could avoid unnecessary irradiation minimizing potential health risks [138], produce hospital cost savings, and reduce the duration of mTBI management in pediatric emergency departments.

TBI in the Military

Based upon the data from a population-based survey of service members and veterans who served in Afghanistan or Iraq, the RAND Corporation estimated that 19.5 % of the previously deployed persons suffered from a "probable TBI" for a total of 320,000 head injury [66]. Between the years of 2005 through 2009 (http://www.health.mil/Research/TBI_Numbers.aspx), a sharp increase in the number of TBI diagnosis, mainly cases of mild TBI, has been reported.

The increased awareness and recognition of the impact of TBI in the military population spurred the interest of US military in a method to objectively determine brain injury and in the development of a point of care test for TBI.

However, in addition to the complexity of TBI, the peculiar characteristics of military setting create another layer of difficulty and complexity in the ability to diagnose TBI [131].

Civilian and the military environments are significantly different. In a civilian setting, following a head trauma, a subject can be quickly transported to the nearest emergency department, where can be promptly evaluated by an emergency physician and undergo a CT or an MRI scan, if is necessary. Conversely, the battlefield is often a very austere environment. In the military setting, the head trauma can occur in remote locations either before, during, or after some type of battle and possibly lasting hours before casualties can be clinically evaluated [131]. Furthermore, evacuation priorities and logistics may impact the ability to evaluate suspected mTBI cases as the ability to image the brain is only located at specific locations in the theater of operations.

Although there is the list of tools to screen casualties such as the Military Acute Concussion Evaluation (MACE) that is well integrated into the military medical evaluation [102], they still rely on self-reporting, may be affected by confounders such stress or fatigue, and may show low sensitivity when administered greater than 12 h [28].

The ideal method for the diagnosis of TBI would be a rapid, definitive, and cost-effective blood-based diagnostic test for TBI. Having such a tool would assist military medics to objectively and quantifiably diagnose the presence and severity of TBI and therefore better provide for the casualty's and assist in making important operational decisions such as allocation of resources and determining when the casualty is fit to return to active duty.

Importantly, the military casualty can and often will experience multiple serious injuries [72, 111]. Thus, the ideal biomarker needs to assess specifically brain injury, and its diagnostic accuracy should be not affected by extracranial injury (i.e., polytrauma). Remarkably, a recent study on moderate-mild TBI (GCS $\geq$ 12) demonstrated that the levels of GFAP in serum were able to significantly differentiate not only between TBI patients and uninjured controls but also between TBI patients and trauma controls (trauma injury without evidence of acute brain injury) [112]. Similar results were demonstrated with serum levels of UCH-L1 differentiating between mTBI, moderate TBI, and uninjured and trauma controls [113].

Furthermore, due to the logistic constraints faced on a battle field, any diagnostic method must meet additional requirements sometimes not faced in civilian medical care and may require different platforms for different levels of care. A *handheld system* would be most suitable for use by emergency medical personnel or personnel deployed in the remote and more austere locations on the battlefield. These systems would ideally use to screen for the presence of TBI, while a small single assay *point of care system* could be used in a field hospital to screen for the presence of mild-moderate TBI and differentiate the level of severity for all TBIs.

Current research and development in the field of brain injury biomarkers give hope the development of an objective diagnostic test for the presence of TBI. Such test will significantly advance the management of civilian patients as well as assist in an accurate evaluation of TBIs experienced by military personal.

Having such a tool would assist military medics to objectively and quantifiably diagnose the presence and severity of TBI, provide advances in objective triage capabilities, and improve clinical management of in-theater TBI. Additionally, it would assist in making important decisions for the casualty's treatment and ultimately affect the long-term health of the warfighters.

Diagnostic Markers of Sports Concussion

It is estimated that between 1.6 and 3.8 million concussions occur annually in the United States [134], and even this estimate may be low, because results of several studies suggest that sports concussions tend to be vastly under diagnosed and consequently poorly managed [96]. This has been a consequence of misconception that concussions are not serious injuries. However, in the past few years, mounting evidence indicates that structural and clinical sequelae are associated with concussions [98, 143]. Most commonly, post-concussive symptoms resolve within a short period (7–10 days), without permanent sequelae, but some athletes can have serious

disabling long-term consequences including prolonged post-concussive symptoms, cognitive impairment, early onset dementia, movement disorders, psychiatric disorders, motor neuron disease, and chronic traumatic encephalopathy [51, 98]. In addition, a catastrophic injury, called the "second impact syndrome," can occur when an athlete who has not recovered from an initial concussion sustains a subsequent blow to the head. The result of this trauma is either significant morbidity or death [162].

Therefore, this increasing awareness has spurred significant efforts to identify individuals with concussion in order to provide appropriate medical care and establish when an athlete can safely return to play after a concussion. Furthermore, it is important to identify individuals who are predisposed to sustaining a concussion or at risk for an adverse outcome after a concussion in order to prevent or at least minimize severe long-term consequences.

At the present time, the only diagnostic tests for brain injury available to physicians are expensive imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI). Unfortunately, these imaging modalities have suboptimal sensitivities for concussion (3–10 % for CT and 10–57 % for magnetic resonance imaging); studies are often not able to confirm mild TBIs and may only identify the very serious injuries that result in swelling and/or bleeding [8].

Therefore, multiple studies have been conducted to identify serum biomarkers that can offer superior diagnostic and prognostic information related to concussions. Furthermore, biomarkers may provide information regarding the molecular pathophysiology of concussive brain injury with practical implications for the management and treatment of athletes who suffered a concussion.

To date limited studies evaluating biomarkers in the setting of a concussion have been conducted, and most of these researches did not specifically evaluate patients with concussion but rather patients with mild traumatic brain injury.

Previous accurate research has shown that S100 has a negative predictive value of 90–100 % for predicting a normal head CT scan and therefore may be used to aid clinicians in emergency settings to determine when to order a CT scan in athletes with mild traumatic brain injury. Regarding the ability of S100B to predict persistent post-concussive symptoms, studies have provided conflicting results. Five studies have demonstrated that elevated levels of S100B are associated to increased incidence of persistent post-concussive symptoms in patients with a concussion [34, 146]. However, several studies were not able to find a significant association between elevated S100B levels and the development of post-concussive symptoms or persistent cognitive or functional abnormalities after a mild traumatic brain injury [8].

In addition, the lack of specificity of S100 for concussion is a major limitation. Elevated levels of S100B have been demonstrated in athletes without concussion who are participating in basketball, soccer, and hockey [140, 141]. Based on the available evidence, S100B does not have adequate specificity to assist with diagnosis of mild traumatic brain injuries in the setting of sports concussion, nor does it provide significant prognostic data related to post-concussive symptoms.

The sensitivity of NSE for mild traumatic brain injury is highly variable [46], and no correlation between post-concussive levels of NSE and persistent post-concussive symptoms was found [46, 139].

The ability of serum cleaved τ protein (CTP) to diagnose mild traumatic brain injury or predict prolonged post-concussive symptoms after concussion has been evaluated in four studies [9, 70]. No significant difference in serum levels of CTP between patients with mTBI and control was found [88]. CTP concentrations did not correlate with prolonged post-concussive symptoms [9, 88], and did not predict abnormal findings on head CT scans in patients with mTBI [70, 88].

The effects of repeated concussions can be potentially debilitating or fatal, if the athletes return to play without allowing enough time for the brain to heal, or they can trigger degeneration of brain tissue leading to very serious consequences such as neurological impairment and chronic traumatic encephalopathy (CTE). A recent study investigated the effects of recurrent head trauma on levels of T-tau, NFL, GFAP, and S100B in CSF of Olympic boxers. CSF levels of brain damage markers were significantly increased after a bout, but also a lack of normalization of NFL and GFAP after the rest period was found. This noteworthy finding supports the hypothesis that the recurrent head trauma in boxing may be associated with ongoing degeneration and potentially with increased risk of chronic traumatic brain injury.

Endocrine Consequences of Mild and Repetitive Head Injury

Traumatic brain injury was recently recognized as a cause of pituitary failure. Despite the evidence of frequent head trauma during sport, it did not draw attention of the medical community until the early 1980s, when the first report was published about the consequences of mild TBI [123]. In the past decade, many studies reported TBI-related hypopituitarism. The severity of endocrine abnormalities is generally related to the severity of head trauma; however, mild TBI can also result in pituitary dysfunction. Hypopituitarism was reported in 37.5 % of patients with mild TBI versus 59.3 % of patients with severe TBI [20]. In a meta-analysis including 1,015 TBI patients from ten cross-sectional and four prospective studies, the prevalence of hypopituitarism after TBI was 27.5 % [133]. The pooled prevalence of hypopituitarism in mild, moderate, and severe TBI was estimated as 16.8, 10.9, and 35.3 %, respectively. Thus, patients with mTBI have lower but substantial risk of hypopituitarism.

TBI can cause acute and late dysfunction of the hypothalamus and hypophysis resulting in partial or complete lack of pituitary hormones. GH and gonadotropin deficiencies are the most common abnormalities. Pituitary dysfunction may contribute to the long-term physical, cognitive, and psychological disability of patients after TBI.

The majority of studies about sports-related head injury published so far focused on the radiological and neuropsychological evaluation. Neuroendocrine abnormalities are poorly investigated. The first report of pituitary function in boxers was published in 2004 [71]. The mean IGF-I levels in boxers (237 ± 23.3 ng/ml) were significantly lower than in the control group (367 ± 18.2 ng/ml). A GH deficiency was found in 45 % of amateur boxers. There was a significant negative correlation between peak GH levels and both the duration of boxing and number of bouts. In another study

where kickboxers were investigated, GH deficiency was found in 22.7 % and ACTH deficiency in 9.1 % of 22 amateur kickboxers. The serum IGF-I level was lower in kickboxers comparing to the control group (276.5 ± 25.9 ng/ml versus 346.9 ± 20.9 ng/ml), and a significant negative correlation was detected between serum IGF-I level and age, duration of sport activity, and number of bouts [151].

The same group of investigators reported pituitary function in 61 amateur boxers. The frequency of GH and ACTH deficiency was 15 and 8 %, respectively. Hypopituitarism was more common in retired (47 %) than in active (7 %) boxers [152]. The authors concluded that (repeated) minor head trauma may have cumulative effects on pituitary dysfunction.

The mechanism of pituitary insufficiency due to TBI is complex and incompletely understood. The specific blood supply may be responsible for the vulnerability of pituitary gland during head trauma. Several mechanisms have been proposed to explain the damage of hypopthalamic-pituitary system such as vascular or mechanical injury, hypoxic insult, compression from hemorrhage, edema, or increased intracranial pressure. All of these mechanisms were supported by the findings of autopsy specimens after fatal TBI [76]. However, the explanations for the common late manifestation of endocrine failures were still questionable. This resulted in a search for other potential mechanisms.

"Lymphocytic hypophysitis" was first described in 1962, and the autoimmune reaction targeting against the pituitary gland has been well documented [48].

Animal studies did also underlie the possible role of autoimmunity in post-TBI endocrine abnormalities [127]. Anti-pituitary antibodies (APAs) were found in 44.8 % of patients with TBI 3 years after the head trauma, while none of the controls were positive for APAs. The ratio of hypopituitarism was higher in APA-positive patients (46.2 %) than in APA-negative ones (12.5 %) [149].

The investigation of boxers supported the hypothesis about the potential role of autoimmunity in the late development of pituitary failure after minor and repetitive head injury. Antibodies were detected against the hypothalamus (AHA) and pituitary gland in 21.3 and 22.9 % of cases, respectively [148]. Interestingly, the ratio of hypopituitarism was significantly higher in AHA-positive boxers (46.2 %) than in AHA-negative boxers (10.4 %). However, there was no significant difference between APA-positive and APA-negative boxers regarding to pituitary insufficiency. The contribution of autoimmune response targeting the hypothalamic and pituitary structures is still unclear, and further investigations are required to clarify the causative role of autoimmunity in the development of post-TBI pituitary insufficiency.

A new, exciting area of research is the role of genetic polymorphisms in the development of CNS disorders. Apolipoprotein E is one of the most abundant proteins in the hypothalamic-pituitary region that plays an important role in the repair of cells following injury. It has three primary alleles (ε2, ε3, and ε4). ApoE-ε3 was regarded as a protective allele, whereas ApoE-ε4 correlated with the poor outcome after TBI [43]. In a recent study, the ApoE-ε3/ε3 genotype decreased the risk of hypopituitarism after TBI; the ratio of hypopituitarism was significantly lower in patients with ApoE-ε3/ε3 (17.7 %) than in those without it (41.9 %) [150].

From the clinical point of view, the major question is which patients with TBI should be screened for pituitary dysfunction. This question has more importance in patients with mTBI because mTBI patients represent the largest group among all TBI patients and nearly half of the patients with mTBI are not hospitalized, and without adequate screening paradigms instituted, they can easily be lost for follow-up. In the consensus guideline published in 2005, all the patients with moderate to severe TBI were recommended to be screened for pituitary dysfunction. The recommendation of Schneider et al. based on the meta-analysis of TBI subjects is the endocrine evaluation of all patients hospitalized for TBI [133]. Preliminary data suggest that ApoE polymorphism and APA positivity may have a predictive value, but more studies with higher number of mTBI patients are needed.

Based on the current data, mTBI patients who need hospitalization for at least 24 h, who have an abnormality on initial CT (fracture, hematoma, brain swelling), and who develop signs and symptoms suggesting hypopituitarism any time after TBI could be suggested to be screened [153].

In the acute phase of TBI, the diagnosis of adrenal insufficiency is the most important because it can be a life-threatening condition. Signs and symptoms of adrenal failure such as hypotension, hypoglycemia, and hyponatremia should be evaluated, and the measurement of basal cortisol is recommended. There is no consensus about the cutoff value of cortisol, but cortisol level <200 nmol/L is highly suggestive of hypocortisolism, and replacement therapy should be initiated. Morning cortisol values between 200 and 500 nmol/L have to be interpreted according to clinical judgment. Glucocorticoid replacement therapy may be indicated if there is any sign of hypocortisolism. The evaluation of thyroid axis using baseline hormones (TSH, fT4, fT3) is recommended in stable condition, before discharge. The measurement of GH and gonadal axes in the acute phase is not proposed because abnormalities may be transient and evidence regarding the beneficial effect of hormonal replacement is lacking [47, 153].

According to recent reports, the early hormonal deficiencies can improve and are not predictors of late disturbances. All pituitary hormonal axes need to be evaluated during follow-up of patients at 3 or 6 months and 12 months after TBI. The assessment of gonadal and thyroid axis does not require dynamic test; basal hormone measurements are sufficient. In premenopausal women with a history of regular menses, no hormonal investigation regarding pituitary-gonadal axis is necessary. To evaluate the pituitary-adrenal axis, dynamic test is usually required unless the basal cortisol level is <140 nmol/L (evidence of hypoadrenia) or >500 nom/L (normal adrenal function). The insulin tolerance test (ITT) is the gold standard method for the diagnosis of ACTH deficiency. However, ITT is contraindicated in patients with epilepsy, CNS disorders, and ischemic heart disease. Glucagon test is an accepted alternative method for the stimulation of pituitary-adrenal axis. Some authors prefer the standard ACTH stimulation test for the diagnosis of secondary adrenal failure. The small dose (1 ug) ACTH stimulation test was also evaluated, and it was found being more sensitive for the detection of partial adrenal insufficiency [132]. The assessment of GH-IGF-I axis is crucial because GH deficiency is the most common endocrine abnormality after TBI. Several dynamic tests are available for this

purpose including ITT, glucagon, GHRH + arginine, and GHRH + GHRP-6 tests [47]. Monitoring of pituitary function in patients with mTBI who do not receive any hormonal replacement therapy is recommended every year up to 3 years [153].

MTBI and Sport

Sports-related traumatic brain injury (TBI) is a common clinical problem with highest number of concussion reported in American football [115].

The relatively high prevalence [74], the usually young age of the athletes, and the potential long-term consequences explain the growing attention this filed attracts. The Centers for Disease Control and Prevention recently issued a warning that concussions in athletes have reached an epidemic proportion in the United States [6, 24].

Establishment of the diagnosis and thereby epidemiological record keeping of sports-related brain injuries is particularly challenging. Those involved in regular sport activities, particularly professional players, report the injury as well as different symptoms seldom or improperly [99]. Their primarily goal is to play again as soon as possible, and long-term consequences are rarely part of such considerations. With growing body of evidence on the consequences of injury, management strategies have been evolving significantly in the last years, drawing increased attention on return-to-play (RTP) decisions and prevention; thus, the proper management of sports-related concussions is also a great challenge for medical professionals [95].

Epidemiology

While among different sport activities concussion/mTBI is a common event, it is substantially underreported. This is well explained by the players' lack of awareness of the symptoms or significance of concussion, their personal drive, and external forces/pressure to continue their participation/playing, and the recognition or fear that reporting a concussion could have adverse professional and financial consequences for the player and/or the team [22, 74, 99].

Each year an estimated 1.7–3.8 million TBIs occur in the United States, causing an estimated cost of 76.5 billion dollars [129]. According to the National Head Injury Association, 18 % of head injuries derive from sports activity [99]. Approximately 71 % of all sports- and recreation-related TBI patients were male [74, 129]. According to a report by the US Centers for Disease Control and Prevention, sports-related brain concussions took an estimated 300,000 per year in the United States [24, 147]. Studies of children and adolescents have suggested that 26 % of closed head injuries in children occur during athletic activities [96, 99].

Sport activities can be divided into two major groups, such as recreational or non-organized sports and organized/sanctioned sports. The former is characterized by a less formal structure, fewer rules, no referees, and less frequent use of protective

equipment; in the second group, there are structured rules regarding training and the games, and these rules are enforced; further, specialized equipment, physicians, and athletic trainers are also available [6].

Participation in contact sports, such as football, ice hockey, soccer, boxing, lacrosse, wrestling, and basketball, carries a risk of mild traumatic brain injury. The risk of concussion is also increased in other activities, such as gymnastics, skiing, sledding, ice skating, rollerblading, cycling, diving, motorcycling, and horseback riding [22, 74, 80, 147].

Athletes do not regularly report on their mild brain injury to their trainers, coaches, relatives, or friends which leads to underestimation of the true incidence of concussion. If investigators asked athletes to report concussions properly, they found higher incidence, ranging from 15 to 45 %. Concussions occur more frequently during games than practices and are six times more frequent in organized sports than in leisure physical activity [96, 99].

Symptoms and Signs

The clinical signs and symptoms of mTBIs may range from minor mood changes to obvious loss of consciousness, which may begin immediately after the injury or several minutes later. The AAN identifies signs of mTBI to be amnesia, behavior or personality changes, confabulation, delayed verbal and motor responses, disequilibrium, orientation, emotional lability, loss of consciousness, slurred/incoherent speech, or a vacant stare. Other symptoms are blurry/double vision; confusion; dizziness; excessive drowsiness; sleep difficulties; feeling hazy, foggy, or groggy; headache; inability to focus or concentrate; nausea; vomiting; photo- or phonophobia; mood changes; emotional outburst; and behavioral changes [6, 73, 80, 129].

The most common symptoms of sports-related concussions are headache (83 %), dizziness (65 %), and confusion (57 %); interestingly, loss of consciousness is observed only in 10 % [74]. The diagnosis and management of athletes suffering a concussion can be difficult, resulting from the nonspecific nature of symptoms and underreporting.

Short-Term Complications: Post-concussive Syndrome (PCS)

In a fraction of patients with sustained mild TBI, persistence of concussion-associated symptoms for more than 4 weeks or their reappearance after 4–8 weeks and/or the development of additional symptoms may occur forming the so called post-concussion syndrome (PCS) [74]. Post-concussion symptoms may develop as a result of a brain injury or from trauma of the head and neck structures [129]. The most common symptoms are persistent headache and dizziness. Other symptoms could be blurred vision, neck pain, fatigue, problems with sleeping, emotional or

cognitive disturbances (irritability, inability to concentrate, memory impairment), tinnitus, vertigo, problems with balance or coordination, and loss of hearing, taste, or smell [129]. There are many factors which may influence the duration, extent, and number of complaints, such as motivation, psychological factors, pending litigation, educational level, and degree of injury [6, 90]. Most of the symptoms are self-limiting and benign, and they usually resolve by 6–8 weeks [6].

Bearing in mind the predominantly self-limited nature of mild TBI and that of PCS persisting post-concussive symptomatology should always call for detailed neuropsychological examinations including detailed analysis of environmental and social factors (litigation, malingering, secondary gains).

It is also well established that PCS-like symptomatology may occur without a history of TBI and can accompany or herald other diseases [81, 119].

Repeated mTBI in Athletes

Following a first concussion, athletes are at increased risk of further concussions, with a peak incidence within the first 7–10 days [74, 99]. Within the same season, the probability for a next concussion is approximately 10 % [74].

Investigations showed that young athletes suffering from three or more concussions had a more severe presentation of concussion, were more likely to have baseline headaches, and were more vulnerable to brain injury [29, 129].

Repeated concussions prior to the complete resolution of a previous TBI may lead to second impact syndrome (SIS) [129]. In this case a reinjury of a still symptomatic patient results in diffuse cerebral dysregulation, which – extremely rarely – can conclude in progressive cerebral edema and subsequent herniation. Children and adolescents are affected more frequently than adults. SIS may result in serious permanent neurologic injury or even death [6, 80, 129].

Studies showed that recurrent concussion of the head may lead to changes of the CSF levels of different biomarkers (NFL, GFAP, T-tau, and S100B), which suggests damages of the brain with different severity (sometimes injury without symptoms) [108].

Long-Term Complications

Chronic Traumatic Encephalopathy (CTE)

Long-term effects of repetitive concussions have been suspected long time ago. The additive effect of multiple sub-concussive (“minimal TBI”) and concussive head impacts may lead to chronic traumatic brain injury.

The clinical symptoms may be presented in different forms, including early difficulty with speech and coordination, the onset of tremor and attention deficits, and psychiatric symptoms. In severe cases pyramidal, extrapyramidal, and severe psychiatric abnormalities may develop [6].

"Dementia pugilistica" is the overall description of the cognitive, behavioral, and motor abnormalities mostly seen in professional boxers who have sustained multiple concussions. Nowadays as an umbrella name, delayed biological effects of repetitive concussions among professional athletes are referred to as "chronic traumatic encephalopathy" (CTE).

CTE includes different symptoms like progressive deterioration in social and cognitive functioning (impaired memory, loss of executive functions, malfunctioning in relationships), behavioral and psychiatric disturbance (paranoia, rampant mood fluctuations, alcohol and drug abuse, major depression with suicidal ideation, suicide attempts, or completed suicide), constitutional symptoms (chronic headaches, generalized body aches and pain, insomnia), and complete switch in habits or attitude like increasing religiosity. Studies showed that the mean age of onset was approximately 42.8 years in American athletes. CTE is characterized by gradual progression which could finally lead to suicide or dementia [74, 98]. Various studies have identified progressive tauopathy as a pathomorphological determinant of CTE [45]. The pathological characteristics of CTE are extensive accumulation of tau-immunoreactive neurofibrillary tangles and astrocytic tangles throughout the frontal and temporal cortices. In advanced cases macroscopic abnormalities can also be detected, including generalized cerebral atrophy (primarily involving medial temporal lobe structures and mammillary bodies) and enlarged ventricles; cavum septi pellucidi, often with fenestrations; and pallor of the substantia nigra [6, 45, 74].

About 17 % of athletes with a history of repetitive concussion, like boxing, develop a "pugilistic" subtype of CTE. The real incidence of CTE still remains unknown. Increased risk is observed in competitive sports such as boxing, soccer, football, hockey, and martial arts [74].

Other Chronic Consequences

Current thought appreciates that TBI is a risk factor for chronic depression, and it plays a substantial role in early development of Alzheimer's disease [108] and Parkinson's syndrome [45]. Investigators found that the prevalence of clinical depression is 11.1 % in retired American football players and demonstrated that there is an increased incidence of depression with higher number of concussions. A history of trauma to the central nervous system is a risk factor for other neurodegenerative conditions too like amyotrophic lateral sclerosis. Different studies showed that sports might also be associated with the development of a motor neuron disease [45].

Recent studies have demonstrated that sports-related repetitive head trauma might induce pituitary dysfunction, especially isolated GH deficiency (*vide supra*). The pathophysiology is not fully known yet, but it is clear that screening of the athletes, who were exposed to chronic repetitive TBI, is necessary [37].

It is also of note that most of the affected athletes are students; thus, the effect of concussions on the young brain may have long-lasting consequences, affecting their later academic performance thereby representing a potentially significant socioeconomical challenge.

Management and Treatment

The amelioration of the care of sports-related injuries and the need of intensified attention to this field are mandated by their frequent occurrence, the predominantly young age of the athletes, and the potential long-term consequences.

While the majority of young athletes consider precautions and strict regulations to be a nuisance, these necessary interventions should serve their well-being, and with time they will be blend into the everyday life.

Care providers should also realize that although taking care of an athlete may not appear different from usual management of an everyday patient, it has some pitfalls that should be kept in mind.

First, a player with suspected mTBI should be removed from the playing field immediately. The on-field assessment is similar to all medical assessments (ABC). Neurological examination should include assessment of the athlete's orientation to person, place, and time. The ability to perform simple tasks and postural stability should be assessed [99]. Transfer to a hospital is indicated in severe cases or if the following occurs or exists: deterioration in consciousness, focal neurological abnormality, confusion or impairment of consciousness for >30 min, loss of consciousness for >5 min, severe or persistent headaches, persistent vomiting, seizures, multiple concussions in the same game or practice session, or athlete with underlying bleeding disorder [6, 115]. After diagnosing a patient, the physical and cognitive stressors should be reduced. Relative cognitive and complete physical rest should be maintained for at least 24 h or until follow-up evaluation with a physician.

A player with a diagnosed concussion should not be allowed to return to play on the day of injury [74, 95].

When an athlete suffers from persistent confusion, lethargy, and focal neurologic signs or there are abnormal findings on the CT scan, hospital admission for further observation or treatment is indicated. Under such conditions, observation is recommended for at least 24 h [80].

In the early post-injury phase, CT is not indicated if adequate observation can be provided; however, in case of prolonged unconsciousness, persistent mental status alterations, or abnormalities on neurologic examination, it is advised to exclude any structural pathology via CT or advanced imaging (*vide infra*) [129].

As it is also alluded to at various points of this chapter, unfortunately under routine care we still lack any specific and highly sensitive marker/measure to define whether the brain injury that has been sustained may require special interest due to high probability of short-/long-term consequences.

Our capability to resolve this problem is – partially – ameliorated by neuropsychological testing. Repeated use of neuropsychological tests before the season and following injury may serve objective information about the mental state of the athlete, and if needed, he or she could be removed from the field before the development of ongoing/permanent symptoms. Further, such an approach may help the follow-up, early recognition, and care of the chronic effects. In the management of the athletes, a baseline examination performed in the preseason is preferred. Orientation,

attention, memory, information processing, and other modalities should be the basis for neuropsychological testing. Neuropsychological examination provides objective information on true brain dysfunction when all other tests, including physical and neurological examination, are normal [6].

Neurocognitive Evaluation of MTBI with Special Focus on Sports-Related Injuries

Mild traumatic brain injury is characterized by several factors that call for novel and specific diagnostic tools or measures.

As psycho-cognitive alterations are associated with mTBI, complex evaluation of the injured should involve specific neurocognitive, neuropsychological testing.

Neurocognitive testing is aimed to measure, quantify, and follow cortical function in patients suffering mTBI and should be considered an integrant part of evaluation and management [6, 87, 90, 115].

Probably the most important field where these tests are employed is the area of sports-related injuries with special focus on avoidance of pronounced deficit potentially associated with repeat injuries. The tests should fulfill the following characteristics: they should be easy to perform and reproducible and should fit the personal profile of the injured [6].

In the literature, we can find different opinions about the use and the usefulness of the results of neuropsychological testing [74, 99]. The results of neuropsychological testing should facilitate the understanding of the effects of injury not only for the athletes but also for the team physicians, trainers, coaches, officials, and parents as well [6]. The tests may include the examination of orientation, attention, memory, and information processing thus ensuring objective data of cognitive function, planning, executive functioning, visuospatial abilities, and visuomotor abilities [115].

The most sensitive parts seem to be information on memory and information processing speed as they recover less rapidly than others. The recurrent use of the tests could influence the results through learning processes. Neuropsychological tests are also influenced by age, education, cultural background, medications, learning disability, sleep deprivation, test anxiety, and previous injuries [115].

Many tests are available for sideline testing, but the question is which to prefer [6]. We can divide the testing materials into paper-pencil and computerized testing methods [31, 74].

Most widely used paper-pencil tests are the Digit Span Test; Halstead-Reitan Neuropsychological Test Battery; Hopkins Verbal Learning Test; Penn State Cancellation Test; Stroop Test; Symbol Digit Modalities Test; Trail Making Test; Vigil Continuous Performance Test; Wechsler Intelligence Tests, Revised; and Wisconsin Card Scoring Test (reviewed in Patel et al. [115]).

Usually it is believed that the first examiner following the medical examination should carry out some cognitive tests as well, like the Post-Concussion Symptom

Scale (PCSS) 20, which is part of the Sport Concussion Assessment Tool (SCAT2) pro forma, Graded Symptom Checklist [22], or Head Injury Scale [27, 74]. For the initial testing of the athletes, there are many different test batteries available such as the Immediate Measurement of Performance and Cognitive Testing (ImPACT), Brain Injury Screening Questionnaire (BISQ), Automated Neuropsychological Assessment Metrics (ANAM), CogSport (formerly Concussion Sentinel), Concussion Resolution Index (CRI), and the Standardized Assessment of Concussion (SAC) [129]. SAC is a tool, which measures orientation, immediate memory, concentration, and delayed recall and also contains neurological examination (recollection of injury, strength, sensation, and coordination) [96, 115].

The use of these self-report tests is not always enough; thus, more complex batteries are needed and recommended to use. The cognitive test needs to serve to evaluate the mental and cognitive state, should be easy to perform, and could be available for sideline assessment [115]. Such sideline assessment batteries are SCAT2 and the Standardized Assessment of Concussion (SAC-part of the SCAT2 proforma) [22, 74, 97].

The Maddocks score (part of the SCAT2 proforma) includes questions about the game [99], rules, or opponent, which are thought to be better in assessing the basic state of the patient than usual questions, such orientation to person, time, and place [74, 92].

It does not need further qualification to perform the test which only takes 5 min. Finally a numerical score will be derived, which could be compared with further/baseline screening results, thus monitoring the recovery of the athletes [115].

Nowadays the most predominantly used tool by sports medicine physicians is the SCAT2 (Sport Concussion Assessment Tool-2). SCAT2 was constructed in Zurich in 2008 during the 3rd International Conference on Concussion in Sport. It was created to develop a standardized tool by adding the preexisting tools together [115]. The popularity of SCAT2 is well explained by the fact that it incorporates parts of other preexisting tests and is based on a large consensus [129].

SCAT2 contains review of subjective symptoms (presence or absence of loss of consciousness or unresponsiveness; seizures or convulsive activities; balance problem/unsteadiness, speech; eye motion and pupils; pronator drift; gait assessment), the Glasgow Coma scale, PCSS, the standardized assessment of concussion (SAC), cognitive assessment (five-word recall; months in reverse order; digits backwards), Maddocks score, and the assessment of balance and coordination [115, 129]. Finally, a score can be derived, but the most useful is when there are baseline and follow-up scores available, because the test does not give a cutoff point for RTP [129].

Some authors recommend that the tests should be repeated at 2–3, 24, 48, and 72 h following the injury [22, 74].

There is an increasing interest for development of computer-based tests specifically constructed for sports-related TBI evaluation such as the CogSport (http://www.cogsport.com), Concussion Sentinel (http://www.concussionsentinel.com), Concussion Resolution Index (http://www.headminder.com), Immediate Post-concussion Assessment and Cognitive Testing (ImPACT© 2.0) (http://www.impact-test.com).

These tests got over the limitations of conventional test materials; however, their main shortcoming is the need for computer access and the time-consuming initial setup [115]

Computer-based test materials are less labor intensive, can be performed in a timely fashion, and are more trustful and sensitive. The results are objective and easier to store and compare with former results. Nevertheless, in cases of severe or moderate concussion, extended neuropsychological examination by a clinical psychologist is needed.

The most frequently utilized computerized test materials are the ImPACT (Immediate Post-concussion and Cognitive Testing) (www. impacttest.com; Pittsburgh, PA, USA) and the "CogSport" test (www.cogstate.com; Melbourne, Vic., Australia).

The ImPACT is composed of six neurocognitive modules (attention, verbal and visual memory and learning, numerical sequencing, speed processing, reaction time). The problem with this test is that it requires a computer screen and a mouse a quiet place, and it needs time (20–25 min) – factors all precluding its application for sideline testing. The CogSport test includes eight parts, which are formulated as card games (reaction time, matching, monitoring, learning). This test does not require any language skills, but it also needs some equipment and time.

Some other computerized test batteries are also utilized, like the Head Minder Concussion Resolution Index (New York, NY, USA) and Automated Neuropsychological Assessment Metric (ANAM; OK, USA).

In the field of sideline care, computer-based testing receives an increasing role. SAC has an electronic version (eSAC – Sideline Assistant, HeadMinder™ Inc., New York, USA) for sideline assessment, applying handheld devices. The collected informations are later synchronized and integrated on the Internet-based computerized neuropsychological assessment tool Concussion Resolution Index (HeadMinder™ Inc., New York, USA) [115].

Sideline ImPACT is another test for handheld sideline assessment and follow-up (ImPACT© Applications, Inc., Hilton Head Island, South Carolina, USA), which is a tool for standardized concussion assessment and can be synchronized with the ImPACT 3.0 computerized neuropsychological assessment tool.

While various studies tried to identify the best test utilized as a single tool, they concluded that the main point is to use the same test as baseline and follow-up testing material [6, 38, 74, 115, 129].

The Zurich consensus guidelines declared neuropsychological testing as the "cornerstone" of TBI identification and management [97]. Different studies showed that the comparison of baseline testing results with post-injury results was more effective in injury detection, than symptom reporting alone [129], but in light of the complex nature of injury, it is also obvious that test results should be evaluated by a physician who should compare them with results of physical and neurological examinations [115].

Treatment

The evaluation and management of an athlete with TBI include symptom assessment, medical examination, and neurocognitive testing. There are no specific medical therapies to treat a sports-related concussion; thereby, while highlighting the issue of the avoidance/prevention of repeated injuries, we should refer to general treatment options listed above. Nevertheless, guidelines do exist to govern the care

for sports-related concussions focusing on physical and cognitive rest until the symptoms resolve, which means usually 2–10 days following concussion. Cognitive rest includes the minimization or avoidance of scholastic work, videogames, computing, and text messaging during the recovery period [74].

Return-to-Play Decision

Nowadays, decisions to let the player return to sporting activities are made on the basis of RTP guidelines. Before constitution of RTP guidelines, athletes returned to the field following a concussion without full recovery, harboring the risk of the development of long-term symptoms and consequences listed above.

In those times instead of the well-being of the athlete, financial or team interests were considered to be relevant, and immediate comeback was forced. Today, long-term well-being of the athletes thus to ensure enough time for recovery became more important. This also came with the recognition that neuropsychological testing is not only a useful tool in the assessment of the injury, but it is also useful in the specification of RTP decisions. To assess the state of the patients according to the changes of physical symptoms is not enough.

To increase healthcare of athletes, RTP guidelines were constructed with the goal to allow full physical, cognitive, and metabolic recovery to the concussed brain.

Contemporary guidelines recognize that in the management of TBI patients, there are some main points, which should be kept in mind. The key feature is physical and cognitive rest until resolving of the symptoms in conjunction with a gradual program of exertion and cognitive workload prior to medical clearance and return to play. Recovery times may be longer in adolescents and children.

The baseline behind RTP criteria is that a concussed brain has a lower threshold of reinjury in the first few days or weeks following the initial injury. An athlete who returns to play within this vulnerable time period risks permanent disability or even death.

Early guidelines (Cantu, Colorado) were based on the severity and number of mTBIs and made RTP decisions according to the symptoms of the athletes [129]. They all included that an athlete with suspected TBI has to be removed from field, and they should not return until the symptoms resolve; if symptoms last more than 15 min or posttraumatic amnesia occurs for at least 1 week, continuous rest is recommended [80].

Later with the increased knowledge about concussions, the management changed, and the RTP criteria became stricter.

The current standard of care is based on the consensus guidelines established at the 3rd International Conference on Concussion in Sport in 2008 (*also see above*). According to these guidelines, there are six phases for RTP. These steps are complete physical and cognitive rest, then advancing to light aerobic exercise (e.g., walking, swimming, stationary cycle), sport-specific exercise, noncontact training drills, and full-contact practice concluding in RTP [95, 97]. The patient should remain asymptomatic in each step to proceed. Unrestricted return to play is permitted when the athlete has progressed through the protocol, is asymptomatic, and has returned to

baseline or normal values on neurocognitive testing. Symptoms of mTBI usually resolve within 1 week; thus, this protocol usually can be completed within a week in adults, while in children it should take substantially more time (14 days) [22, 74, 129]. If any symptom appears, the athlete has to return to the former phase until resolution for at least 24 h. It is necessary that the patient should stay asymptomatic without using any medications, which could alter their symptoms and signs [33].

The Zurich consensus guidelines include some other factors, in which cases further examinations are needed; these are prolonged duration of symptoms, prolonged LOC, seizures, multiple mTBIs especially in the recent past, or change in mental health.

Prevention

The prevention of athletes with mTBI has different approaches.

In the United States, to increase the protection of the athletes and to standardize medical care, federal and state governments, along with sport's governing bodies, try to renew rules and policies [129].

Proper identification and management of sports-related concussions may be the best prevention [99]; thus, an important point is that coaches, trainers, players, and family are also educated about the possible signs and symptoms to ensure early recognition [6, 74, 129].

The conditioning of neck muscles could avoid the acceleration of the head during impact [6, 99, 115].

The use of helmets and of the prescribed, protective equipment decreases the risk suffering an injury. Therefore, there is a huge responsibility on the shoulders of the sporting goods factories in developing of the different equipments, and, actually, manufacturers and researchers continuously focus on helmet redesign (weight, size, materials) [6, 83].

Helmets are of particular importance as far as prevention is considered. This hard outer shell is designed to spread the force of impact over a large surface area while also preventing scalp injuries; second, its inner layer, often with an advantageous web or suspension design, helps to dissipate the kinetic energy of the acceleration forces by an energy-absorptive mechanism [6, 83].

It is thought, that mouthguards decrease the appearance of intraoral injuries, and they may decrease the possibility of a concussion. It was shown that also the wear of a face shield may reduce the impact to the head [6].

Conclusions and Proposals for Future

Despite the large number of highly debated factors associated with mild TBI, its significance is obvious: there is a large number of patients affected; thereby, accidental failures of triage can be associated with major consequences. Compelling evidence points to the importance of post-concussive syndrome which again

primarily because of the bulk of patients affected can represent an epidemiological problem. Repetitive (sports-related) injuries represent a major challenge particularly as the safe/optimal time for rest and return to play/work has to be defined.

Future research should focus on more efficient triage probably involving biomarkers to identify those cases who necessarily require imaging and the ones who may suffer from transient or permanent long-term sequelae of mild TBI. A more appropriate tool to assess the optimal time to return to play/work should also be defined. Likewise the selection of adequate, fast, easily, and reliably repeatable cognitive tests should also help the diagnosis and triage. Similar to the case of more severe forms of TBI in mild TBI, the significance of endocrine alterations as well as their role in long-term sequelae should be elucidated.

Last but not least, future research should clarify the association of mild/repetitive TBI and CTE-/Alzheimer-related late cognitive decline.

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