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Iatrogenic Hypothalamic Disorders

22

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Non-surgical Iatrogenic Hypothalamic Disorders

The hypothalamus is a small structure that is packed with neurons that interface with various structures in the brain and control diverse functions in the human body. Various medications can affect hypothalamic function by modulating the activity of neurotransmitters or by causing structural damage. Multiple medications can cause similar effects on the hypothalamic-pituitary-adrenal axis. The iatrogenic effects of these medications can be classified according to the specific hypothalamic dysfunction they may cause. Knowledge of the various pharmaceutical hypothalamic affectations should guide decision-making on its administration and discussion with patients and family regarding adverse effects.

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Hyperprolactinemia

Prolactin is a hormone secreted by lactotrophs located in the anterior pituitary gland, which facilitates lactation. Dopamine (D2) receptors in the tuberoinfundibular area are one of the most important aspects of prolactin regulation through the tuberoinfundibular dopaminergic system [1]. *Hyperprolactinemia is classically defined as detecting prolactin level more than 20 ng/ml in men and greater than 25 ng/ml in women at least 2 h after waking up in a fasting state* [2]. *The basic mechanism for hyperprolactinemia involves either eliminating or reducing inhibitory pathways or through direct stimulation of lactotrophic prolactin production* [3]. *Hyperprolactinemia is characterized by amenorrhea and galactorrhea in women, and in men, low libido and fatigue predominate* [4, 5].

Antipsychotics

Antipsychotics have been the foundation of schizophrenia therapy since the advent of chlorpromazine use 50 years ago [1]. These groups of medications are the most common ones to induce hyperprolactinemia, and their most common adverse effect is hyperprolactinemia [5]. The antipsychotic efficacies of the older antipsychotics (chlorpromazine, thioridazine, fluphenazine) have been shown to be directly proportional to their prolactin-raising potency [6–9]. These classical antipsychotics affect all

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dopamine pathways involved in prolactin regulation because they are not selective [3]. Of the classical antipsychotics that include butyrophenones, phenothiazines, thioxanthenes, and pimozide that cause early and sustained prolactin increase during therapy, it is worth mentioning that flupenthixol deviates from this profile in that after the first increase above baseline in the first month of therapy, prolactin level normalization has been found more than 6 months after continued use [10, 11].

Atypical antipsychotics are known for improved antipsychotic effect and adverse event profile [3]. Possible explanations for this pharmacologic profile include receptor binding specificity, regional dopamine receptor preference, different D2 receptor affinity, combined dopamine agonistic and antagonistic activity, and combined antagonism of dopamine and serotonin receptors [3, 11–14]. Of the newer antipsychotics, risperidone has a significant prolactin raising potency [3] and can potentially be mistaken for a prolactinoma. Therefore, it is crucial to establish an accurate timeline of symptoms and risperidone use, as this may help avoid unnecessary imaging or treatment [15–17]. Clozapine, olanzapine, ziprasidone, and aripiprazole not only bind weakly but also have antagonist-agonist effect at the D2 receptor [18–22]. Consequently, with these medications, prolactin levels rise transiently and return to baseline within 8 h [23, 24].

Antidepressants

Significantly less common than antipsychotics, antidepressant medications by which their mechanism of action is through serotonin activity can cause asymptomatic hyperprolactinemia [5, 25]. Tricyclic antidepressants (TCA) have been known to cause modest hyperprolactinemia. Clomipramine raises prolactin levels by 60% in men and 87.5% in women [26]. The monoamine oxidase (MAO) inhibitors, pargyline and clorgyline, have been shown to increase prolactin levels by 5.8 and 8.6 ng/ml, respectively [27]. Selective serotonin reuptake inhibitors (SSRIs) have not been known to be associated with hyperprolactinemia [28].

Opiates

Opiates inhibit dopamine release from the hypothalamus and cause hyperprolactinemia indirectly by inhibiting prolactin-inhibiting factor release or stimulating prolactin-releasing factor production [29]. This effect of opioids is mediated via the μ receptor [30]. It has also been reported to control prolactin secretion through its action on the synchrony of pulsatile pattern of prolactin [31]. Morphine and morphine analogs cause a persistent rise in prolactin levels, whereas methadone use results only in transient elevations [32].

Antiemetics or Prokinetics

Metoclopramide and domperidone are dopamine antagonists used for the treatment of nausea, vomiting, or decreased gastric motility. Through their dopamine antagonistic mechanism, they prevent dopamine from binding to the D2 receptor and result in hyperprolactinemia [3]. Around half of the patients taking these medications develop hyperprolactinemia and present with amenorrhea, decreased libido, and galactorrhea [33, 34].

Antihypertensives

Alpha-methyldopa acts as a false neurotransmitter and prevents L-dopa conversion to dopamine leading to dopamine synthesis decrease [35]. Reserpine on the other hand affects dopamine hypothalamic storage [36]. Verapamil acts on the neuronal N-type calcium channel and inhibits the production of dopamine from the hypothalamus via an unknown mechanism [37]. This inhibition of dopamine results in hyperprolactinemia [37]. Romeo et al. studied 449 subjects on verapamil and observed that 8.5% of them developed hyperprolactinemia compared to 3% in the control group [38]. A common beta-blocker used for emergent blood pressure control is labetalol that may cause hyperprolactinemia via central pathways as it was shown that dopamine agonist pretreatment decreases prolactin response [39].

H2 Receptor Antagonists

Cimetidine and ranitidine stimulate prolactin secretion [3, 40, 41]. Notably, cimetidine has

been found to decrease hypothalamic dopamine release [42] and also acts on neurotransmitters such as pituitary GABAergic system [43].

Cholinomimetic Medications

It has been shown that peptide modulation of the hypothalamic-pituitary regulation of prolactin plays a role in the increase in prolactin after intravenous infusion of physostigmine, a cholinomimetic medication [44]. It was reported that cholinergic stimulation of beta-endorphins in the hypothalamus was associated with prolactin level increase [44].

Hypopituitarism

Hypopituitarism is the general decrease of pituitary hormone production which can be due to tumors, inflammation, infection, infarction, or autoimmune conditions or as a complication of medication or surgical procedures. Because the hypothalamus primarily exerts control over the pituitary gland, any medication affecting the hypothalamic function may in turn result in hypopituitarism.

Immune Checkpoint Inhibitors

Immuno-tolerance is achieved by co-stimulatory pathways involving the programmed death-1 receptor (PD-1) and its ligand (PD-L) and the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [45]. The PD-1/PD-L pathway inhibits the activation and proliferation of T cells and stops the production of cytokines [45] while cell cycle arrest and cellular death in regulatory and activated T cells [45–47]. The CTLA-4 pathway binds on CD28 molecules with B7-1 (CD80) and/or B7-2 (CD86) molecules on the antigen-presenting cell (APC) surface in lymph nodes, which is the early stage of T cell activation [45]. The PD-1 pathway on the other hand affects the last part of the immune response, by binding to PD-L1 and programmed death ligand 2 (PD-L2), in peripheral tissues and blocks T cells [48]. Its adverse effects, including endocrinopathies, are related to its immune-mediated effects [45]. These immune checkpoint inhibitors (ICIs) may cause dysfunction of self-reactive quiescent T cells [49]. Secondary adrenal insufficiency due to failure of the hypothalamic-pituitary axis has been reported [50, 51]. Pituitary hypophysitis can present due to symptoms associated with the hormonal deficiencies or actual mass effect from the gland [50]. Direct hypothalamic involvement can be due to mass effect or direct autoimmune dysfunction that may present as panhypopituitarism as well. A high index of suspicion is needed as the presentation may be subtle until severe crisis occurs. ICI-induced hypophysitis affects the corticotrophs, gonadotrophs, thyrotrophs, and rarely lactotrophs [52]. The incidence of hypophysitis with ICIs is 0.4–1.7%. The highest rate is noted with ipilimumab (5.6%), followed by tremelimumab (1.8%). Nivolumab and pembrolizumab have a hypophysitis incidence of only 0.5% [53]. The mechanism of ICI-induced hypophysitis is unclear; however, complement activation by the antibodies could play a role. This also may explain the higher incidence of hypophysitis seen with ipilimumab as it is an IgG1 antibody that can activate the complement pathway [54]. Hypophysitis presents 4–10 weeks after treatment. Clinical features include headache, weakness, and fatigue. Pituitary hormonal evaluation could show a low adenocorticotrophic hormone (ACTH), cortisol, free t4, luteinizing hormone (LH), and follicle stimulating hormone (FSH). MRI of the pituitary gland may show an enlarged pituitary with homogenous or heterogeneous enlargement; however, a normal appearance of the pituitary gland does not rule out hypophysitis [55, 56]. Treatment with high-dose glucocorticoids is initiated when there is a mass effect or visual defects.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Vasopressin or antidiuretic hormone (ADH) is synthesized in the hypothalamus and is stored in the posterior pituitary. ADH is secreted in response to an increase in osmolality detected by the osmoreceptors in the anterior hypothalamus [57, 58]. *Its criteria were first established about 40 years ago* [59] *and include hyponatremia, low*

plasma osmolality, high urine osmolality, and high urine sodium in the absence of volume depletion and normal renal and adrenal function. Its clinical manifestation depends on the acuity and severity of hyponatremia and may present as lethargy, cramping, anorexia, nausea, vomiting, seizures, coma, and death [57]. *It is treated by fluid restriction, salt tablets, or V2 receptor antagonists* [60]. *SIADH can be caused by a several groups of medications.*

Diuretics

Thiazide diuretics are one of the most common causes of hyponatremia [61]. The exact mechanism of thiazide-induced hyponatremia is unclear; however, the proposed mechanisms include increased secretion of ADH via direct stimulation [57, 62, 63] or indirectly by inducing hypovolemia. Hypokalemia may also increase osmoreceptor-mediated release of ADH [57, 64]. Old age, female gender, and low body mass are risk factors for the development of thiazide-induced hyponatremia [57, 65].

Antidepressants and Antipsychotics

Antidepressants (SSRI and TCA) and antipsychotics (phenothiazines and butyrophenones) have been associated with hyponatremia associated with SIADH by increasing the release of ADH [57, 58]. The incidence of hyponatremia is highest with SSRIs ranging from 0.5% to 32%. However, care must be taken to rule out primary polydipsia, which is co-prevalent with psychiatric disorders before making the diagnosis of SIADH [66, 67].

Carbamazepine and Oxcarbazepine

Used for partial and generalized seizures, mood disorders, psychotic disorders, and trigeminal neuralgia, carbamazepine and oxcarbazepine can both increase the secretion of ADH. The incidence of hyponatremia with carbamazepine is 4.8–41.5% and correlates with the dose and serum level of the same [58, 68, 69].

Antineoplastic Agents

Cyclophosphamide causes hyponatremia secondary to the release of ADH. Patients on cyclophosphamide therapy are advised to drink lots of fluids to prevent the development of hemorrhagic cystitis, and this can lead to severe hyponatremia [70, 71]. Other antineoplastic agents that are associated with SIADH include vincristine, vinblastine, and cisplatin [72–74].

Opiates

Opiates cause SIADH due to direct stimulation of ADH as well as indirect stimulation due to opiate-induced nausea and hypotension [26].

Sulphonylureas

Chlorpropamide, through its direct action to increase ADH production centrally, and stimulation of adenylate cyclase generation or inhibition of cyclic adenosine monophosphate at the level of the kidneys, result in increased ADH effect, and antidiuresis is produced [75].

Impulse Control Disorders

The hypothalamus, along with several other regions of the brain, is involved in controlling behavior. Stimulation of the ventral region of the hypothalamus results in aggression, while the lateral hypothalamic neurons have a role to play in controlling impulses [76, 77]. Impulse control disorders such as pathological gambling, hypersexuality, and compulsive shopping have been reported with the use of dopamine agonist therapy for the treatment of Parkinson's disease, restless leg syndrome, or hyperprolactinemia [78]. Moore et al. studied 1580 events of impulse control disorders and observed a strong association with the use of dopamine agonists. The association was strongest for pramipexole, ropinirole, and aripiprazole, which had a preferential affinity for the D3 receptor [79].

Drug-Induced Hyperthermia

Control of the body temperature is within the hypothalamus. The anterior hypothalamus receives and processes the afferent information, while the posterior hypothalamus initiates

efferent responses based on the input from the anterior hypothalamus. A number of different neurotransmitters, including norepinephrine, dopamine, prostaglandin, and neuropeptides, play an important role in the mediation of temperature [80, 81].

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare and potentially fatal complication of drugs that can block dopamine receptors most especially those that block D2 receptors [82]. Hyperthermia, a part of the syndrome, can specifically be explained by the hypothalamic pathway [82]. Antipsychotic medications are the most common cause of NMS. However, it can also occur in association with prochlorperazine, metoclopramide, and droperidol [83–85]. NMS is secondary to the depletion or blockade of dopamine in the hypothalamus, which results in decreased heat loss and increased heat production. The hallmark of NMS is muscular rigidity and hyperthermia with a history of neuroleptic medication. Other symptoms include diaphoresis, dysphagia, tremors, incontinence, mutism, and labile blood pressure. The onset of NMS is typically 24 h after the drug has been taken [86, 87]. Management includes supportive measures to achieve normothermia and administration of bromocriptine and dantrolene [88].

Sympathomimetic Syndrome

The thermoregulatory function of the hypothalamus can be affected by noradrenaline (norepinephrine), serotonin, or dopamine [89–91]. Increased heat production by peripheral acting medication causes a sympathomimetic syndrome that is life-threatening and implicates 3,4-methyl enedioxymethamphetamine (MDMA/ecstasy), amphetamine, or cocaine [91]. These sympathomimetic substances are believed to cause alteration in the levels of norepinephrine, dopamine, or 5-hydroxytryptamine, thereby affecting the hypothalamic-pituitary regulation of temperature. Clinical features include agitation, confusion, and hallucinations and quickly progress to status epilepticus and death. Other features include myocardial infraction, disseminated intravascular coagulation (DIC), and renal failure. Management consists of aggressive cooling, anticonvulsants, and benzodiazepines for agitation [88].

Other Medication-Induced Hypothalamic Disorders

Estradiol treatment has been shown to affect beta-endorphin neurons in the arcuate nucleus selectively [92].

Amphetamines have been found in animals to induce hyperphagia and subsequent obesity via lateral hypothalamus injections as a local neurotoxic effect [93].

Surgical Iatrogenic Hypothalamic Disorders

Iatrogenic hypothalamic injuries during neurosurgical procedures can cause devastating consequences and should be on the forefront of every neurosurgeons' mind when operating within the vicinity of the hypothalamus and its surrounding structures. Although hypothalamic damage is rare, the resulting functional outcome may be devastating and may affect a patient's quality of life [94, 95]. The general mechanisms of complications lie with the surgical approach to the sellar and suprasellar region and the manipulation of the hypothalamus in association with the pituitary gland and the optic structures [95, 96], most especially in cases when mass lesions are strongly adherent to the hypothalamus [94].

Neurosurgical Anatomy Considerations

As a minute structure with a volume of 4 cc containing multiple functional nuclei and fibers, located at the base of the brain [97–99], its preservation during neurosurgical procedures cannot be overstated. More specifically, it is under the thalamus separated by the hypothalamic sulcus of Monro, lying on the wall and floor of the third ventricle, bordered by the lamina terminalis, a

gray matter layer above the optic chiasm anteriorly, and by the periaqueductal gray matter and the brainstem tegmentum posteriorly [100–102]. It is composed of several distinct nuclei with widespread neural interconnections within the brain and governs many of the human body's homeostatic, regulatory, and motivational behaviors (Fig. 22.1). Along the rostro-caudal axis, the distinct hypothalamic areas based on nuclei-anatomical landmarks include the anterior (supraoptic, pre-optic, or chiasmal) region located above the optic chiasm, medial (tuberal or infundibular) region located above the tuber cinereum, and posterior (mammillary) region [97, 100–102]. Mediolateral divisions include the periventricular, medial, and lateral zones [97, 101, 102]. Generally, the anterior region with the supraoptic nucleus produces vasopressin, while the suprachiasmatic nucleus is involved in the circadian rhythm [100–102]. The medial region is associated with controlling habits of eating and feeling of satiety, secretion of orexigenic peptides, and other motivational behaviors [100–102]. Whereas, the posterior region is involved in feeding behavior, gastrointestinal motility, cardiovascular regulation, learning, thermoregulation, memory, and emotions [100–102]. This brief anatomical overview demonstrates the value of taking perioperative caution and ultimately for understanding the following outcomes of various hypothalamic brain injuries that can occur intraoperatively.

History of Neurosurgical Approaches

The first transsphenoidal surgery for pituitary surgery was done in 1907 by an Austrian surgeon named Hermann Schloffer [95, 103–106]. This approach leads to the development of the endonasal and sublabial approaches [95, 106, 107]. Subsequent approaches including endonasal transseptal transsphenoidal approach and transnasal/submucosal approach were then performed [95, 104, 106, 108, 109]. A French neurosurgeon named Guiot combined the transsphenoidal approach with intraoperative fluoroscopy and introduced this approach to Jules Hardy, a Canadian surgeon, in 1965 [95, 106]. Hardy then incorporated the operating microscope to the use

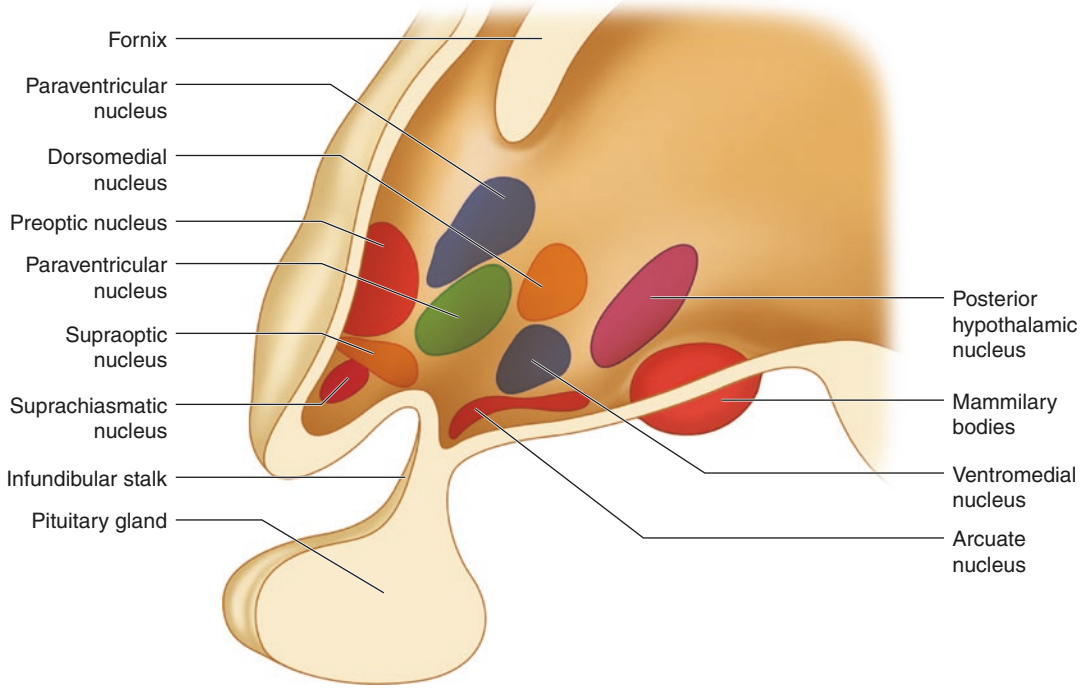

Fig. 22.1 Hypothalamus and its nuclei. (With permission Pop et al. [100])

of fluoroscopy [95, 106, 110, 111]. Neurosurgical approach via endoscopy was first utilized in 1806 for paranasal approaches [95, 112] and did not gain ground until the 1990s when there was an improvement in techniques and instrument technology [113]. Jankowski utilized the endoscopic endonasal approach for pituitary adenoma resection for the first time in the 1990s [95, 106, 114–117]. This approach allowed neurosurgeons to have a closer magnified view of the ventricles from within its walls [118]. Its initial use was mostly for hydrocephalus [119], but currently, this approach has expanded to skull base surgery [119, 120]. Carrau et al. reported the first application of neuroendoscopy for skull base tumors with their publication on endonasal transsphenoidal hypophysectomy [118, 121]. The use of the operating microscope improved microsurgical techniques by increased magnification and illumination [120], and as the years passed, in addition to this, new techniques, neuronavigation and intraoperative imaging, broaden the range of lesions that can be resected [120, 122].

Risk of hypothalamic injury during these surgeries is increased with suprasellar extension. This is common with macroadenomas and craniopharyngiomas [95, 123–125]. Although pituitary adenomas are the most common types of tumors approached surgically, the invasive behavior of craniopharyngiomas should be highlighted because several prognostic factors are considered based on hypothalamic involvement preoperatively. Hyperphagia, obesity, and behavioral dysfunction [126–129] are more commonly seen in craniopharyngiomas than as part of pituitary tumor extension. The same is true for malignant tumors of the suprasellar region.

Neurosurgical Approaches

Transcranial Surgery

Historically, transcranial approaches have been the most common approach to surgical resection in the sellar/suprasellar region prior to the introduction of transsphenoidal techniques, initially microscopic and later endoscopic. For pituitary adenomas, the vast majority of cases are now done transsphenoidally; however, there is still a role for transcranial surgery for other pathologies, such as craniopharyngioma, hypothalamic tumors, and intraventricular tumors. Several transcranial approaches have been described in literature. The most common approaches to the suprasellar region are the subfrontal and pterional (frontosphenotemporal). Transventricular approaches (micro- or endoscopic) are used for resection of intraventricular and primary hypothalamic tumors [130–133]. The pterional approach is the most commonly used transcranial approach [95]. This approach starts with a curvilinear incision from the root of the zygoma following the hairline toward the midline and extended contralaterally as necessary. Most commonly, a myocutaneous flap is elevated, and if further temporal exposure is needed, a sub-fascial dissection can be performed to reflect the temporalis muscle posteriorly. The craniotomy is centered around the "pterion," which is the confluence of the frontal, sphenoidal, and temporal bones. After the craniotomy is elevated, depending on the sites of the lesion, the Sylvian fissure might or might not need to be opened. Another common approach is the subfrontal, which is similar to the pterional, but the craniotomy advances more into the frontal bone and includes more elevation of the frontal lobe than the temporal side. This exposure is used more for tumors that are purely suprasellar. A progression of these approaches is the orbitozygomatic craniotomy, in which the orbital rim is removed to facilitate superior visualization of tumors with a very large suprasellar component, which are located in the third ventricle. In general, transcranial approaches to the suprasellar region are preferred for tumors such as craniopharyngiomas, meningiomas, and pituitary tumors of fibrous or invasive nature. The degree of suprasellar extension is not so much a limitation for transsphenoidal surgery any more since the advent of endoscopic techniques. More and more tumors that were considered nonoperable through a transsphenoidal route can now be resected via an endoscopic transsphenoidal approach. For tumors of the third ventricle and primary tumors for the hypothalamic region, such as gliomas or hamartomas, transventricular

surgery can be considered. This can be accomplished with a microscope or endoscope. The most common microscopic approaches are interhemispheric transcallosal and fronto-transparenchymal approaches. Intraventricular endoscopy can be used to biopsy and resect some types of tumors. Some hypothalamic tumors, such as hamartomas (which are non-neoplastic in nature), can cause intractable seizures, and in those cases, surgical resection can be considered. This area can be approached through transventricular or subfrontal/pterional routes. However, with the present-day introduction of laser interstitial thermal therapy (LITT), these tumors can be treated in a minimally invasive fashion with excellent results [134].

Transsphenoidal Surgery

The transsphenoidal route is the most used for the resection of pituitary adenomas. With the introduction of endoscopy, however, the indications for transsphenoidal surgery have been expanded to multiple pathologies that once could not be treated through this route. Currently, two different techniques are used for transsphenoidal approaches. One includes using the operating microscope and a retractor system to access the sella through the nose. The second one uses endoscopes, which improve visualization and illumination of the sellar region.

Transsphenoidal Microscopic Surgery

Since the introduction of the operative microscope and fluoroscopic guidance in transsphenoidal procedures in the 1960s [111, 135, 136], this technique became the most used among neurosurgeons for resection of sellar tumors. Many surgeons have adopted the use of endoscopes; however, microscopic techniques are still broadly used. Advantages of the microscope include faster access to the sella, three-dimensional view of the anatomy, and ability to use the microsurgical techniques that most neurosurgeons are familiar with. The drawbacks include limited illumination due to poor light penetration, in a narrow oxford, deep exposure, and limited field of view, which doesn't allow panoramic visualization of the sella [137]. Several studies have compared outcomes for pituitary adenomas between microscopic and endoscopic techniques, and no significant difference in outcomes has been found for tumors with minimal or no suprasellar extension. Endoscopy does appear to increase the extent of resection for larger tumor with significant suprasellar extension [138].

For the microscopic techniques, the main principle involves creating submucosal access to the sphenoid sinus, which can be accomplished via sublabial or intranasal, septal mucosal incision. The sublabial technique has been for the most part abandoned due to increased patient discomfort and the risk of complications, such as numbness and paresthesias in the upper lip and teeth [139]. In the endonasal approach, the mucosa over the cartilaginous septum is injected with lidocaine with epinephrine, and a small vertical incision is made. The mucosa is then dissected back to the rostrum of the sphenoid bone. A transsphenoidal speculum is introduced, and the vertical plate of the ethmoid is fractured to the contralateral side. This allows for the blades of the speculum to open, thus exposing submucosally the front of the sphenoid sinus. Adequate position of the retractor system can be verified using intraoperative fluoroscopy or navigation. The sphenoid ostia are identified, and the entire front of the sphenoid sinus is removed with Kerrison punches. The top of the vomer bone is removed as well. The sphenoid sinus usually contains one or more septations, which need to be removed. The anatomy is identified based on the preoperative imaging and navigation. In most cases, an infrasellar recess can be identified. It is important to be aware of where the midline is to avoid injury to the carotid or cavernous sinuses when opening the sella. In case of large tumors, the bone of the sella is usually eroded, and upon removal of the sphenoid mucosa, the thin layer of the bone can usually be easily elevated with a dissector. If the bone is thick, a drill might need to be used to open the anterior wall of the sella. Once the bone over the anterior portion of the sella is removed, the dura is cauterized and opened sharply. Pituitary adenomas tend to be soft and can be delivered using ring curettes and suction. For fibrous tumors, an ultrasonic aspira-

tor can be used as well. Once the tumor is removed, the distended diaphragma sellae will drop into the sella under the pressure of the intracranial cerebrospinal fluid. Once this occurs, the surgeon can be confident that the suprasellar tumor has been removed. The tumor must be removed in a specific sequence, inferior and posterior portions first, to prevent early descent of the diaphragm which would obliterate the field of view. If the diaphragm doesn't drop, the surgeon cannot know for sure if the suprasellar portion of the tumor has been completely removed. This is where the use of endoscopes has an advantage, since angled lenses can be used to visualize the suprasellar component of the tumor.

Once the resection is complete, the sella can be packed with fat and reconstructed with a piece of vomer or a synthetic plate. Once the speculum is removed, the mucosa is re-approximated onto the septum, and nasal packing is applied to keep the mucosa in place. If residual suprasellar tumor is identified in postoperative imaging, options include to wait and see if the suprasellar component will eventually descend, perform a second transsphenoidal approach, consider a transcranial approach, or use of endoscopy. If a large portion of tumor is left in the suprasellar space, it can turn into a hemorrhagic mass, causing increased mass effect and edema in the optic apparatus and hypothalamus during the postoperative period, leading to deterioration of the patient [123].

Transsphenoidal Endoscopic Surgery

In the past two decades, there has been a shift toward transsphenoidal endoscopic surgery from microscopic surgery [140]. This approach offers improved illumination and visualization of the anatomy through its panoramic, wide-angle view. The introduction of endoscopy has expanded the indications of transsphenoidal surgery and has even changed the surgical management of some skull base pathologies. The main advantage of the endoscope is improved illumination and visualization with the ability to use angled lenses to "look around the corners," which, in combination with angled instruments, allows to reach tumors beyond what is possible with a microscope. Disadvantages include loss of three-dimensional vision, which requires a steeper learning curve from the surgeon, and a more involved access to the sella which often necessitates the collaboration of an ears, nose, and throat (ENT) surgeon. Extended approaches to the sellar and suprasellar region have been described to treat large tumors with suprasellar, hypothalamic, and third ventricular involvement. The main complication seen after resection of these large tumors through a large skull base defect has been cerebrospinal fluid fistula. The development of vascularized nasal septum mucosal flaps has allowed for this complication to become less frequent [141].

The patient is positioned supine with the head elevated above the level of the heart to decrease bleeding. Intraoperative navigation is commonly used (Fig. 22.2). An irrigating sheath helps keep the lens clean.

A zero-degree endoscope is advanced through the nostril. The middle and superior turbinates are outfractured to expand the corridor. The ostium of the sphenoid is identified and expanded. A bi-nostril approach is favored by most surgeons. This involves resection of the posterior portion of the nasal septum, which allows the surgeon to use bimanual technique introducing instruments through both nostrils. A wide sphenoid sinus opening is performed, and the septations in the sinus are thoroughly removed. The endoscope allows for close inspection of the anatomy of the sphenoid sinus. The main ana-

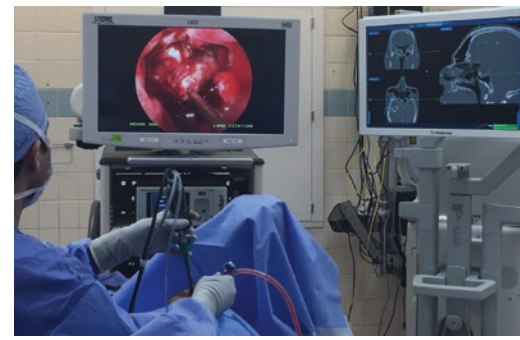

Fig. 22.2 Operating room setup for endoscopic transsphenoidal approach. A bi-nostril approach with posterior septectomy is used. The surgeon is holding a navigated suction on the right hand, showing the anterior wall of the sella. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

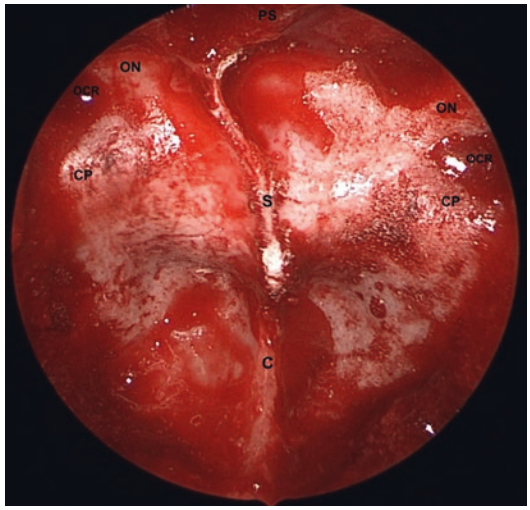

Fig. 22.3 Endoscopic view of the posterior wall of the sphenoid sinus after a wide sphenoidotomy and removal of septations. C clivus, CP carotid prominence, ON optic nerve, OCR optico-carotid recess, PS planum sphenoidale. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

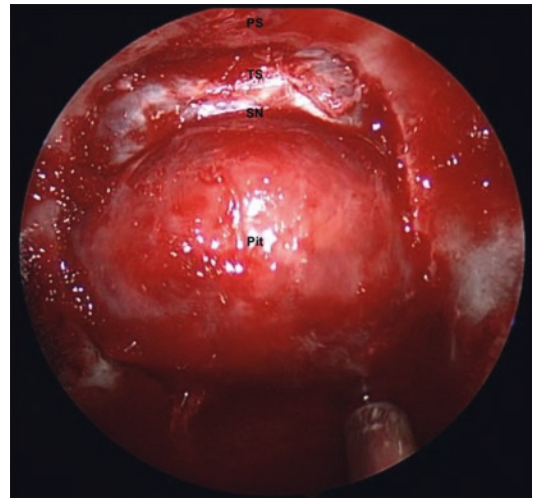

Fig. 22.4 Endoscopic view of the sellar region after bone removal. Pit Dura over the anterior pituitary, PS planum sphenoidale, SN suprasellar notch, TS tuberculum sellae. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

tomical landmarks are the infrasellar recess, carotid prominences, optic canal prominences, and optico-carotid recesses (Fig. 22.3).

Similar to the microscopic technique, the bone over the sella is removed all the way to the cavernous sinus on either side. For tumors with limited suprasellar extension, the bone removal stops at the level of the tuberculum sellae. If the tumor has a large suprasellar component, the tuberculum is removed and as much planum sphenoidale as needed (Fig. 22.4).

Once the dura is exposed, the position of the carotid arteries can be confirmed using Doppler and/or navigation. The dura is cauterized and opened sharply (Fig. 22.5). In microadenoma surgery, heavy venous bleeding is usually encountered from the intercavernous sinus. This can be controlled packing with hemostatic agents. Adenomas which enlarge the sella usually displace and obliterate the intercavernous sinus, so dural bleeding is usually not an issue.

Pituitary macroadenomas are removed using the same techniques described for microscopic surgery. Resection of microadenomas often requires incision of the normal pituitary (Fig. 22.5). Extracapsular dissection is preferred

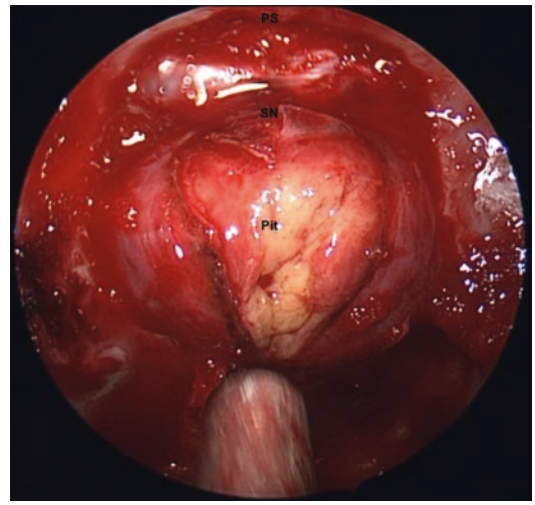

Fig. 22.5 The dura over the pituitary gland has been opened. Note the normal, yellow-colored pituitary gland. Pit pituitary gland, SN suprasellar notch, PS planum sphenoidale. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

for these tumors, especially when they are functioning, to ensure complete resection [142].

Firm adenomas, craniopharyngiomas, meningiomas, and other tumors of fibrous consistency require a different dissection strategy. In these cases, additional bone is removed, and the dura is

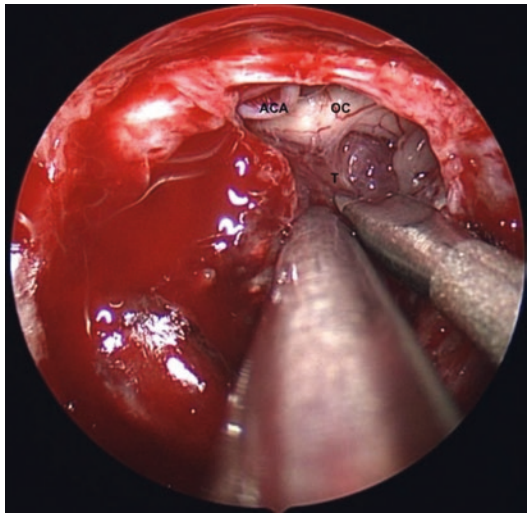

Fig. 22.6 Dissection of the tumor from the optic chiasm. The pituitary gland is being retracted inferiorly. OC optic chiasm, ACA anterior cerebral artery, T tumor. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

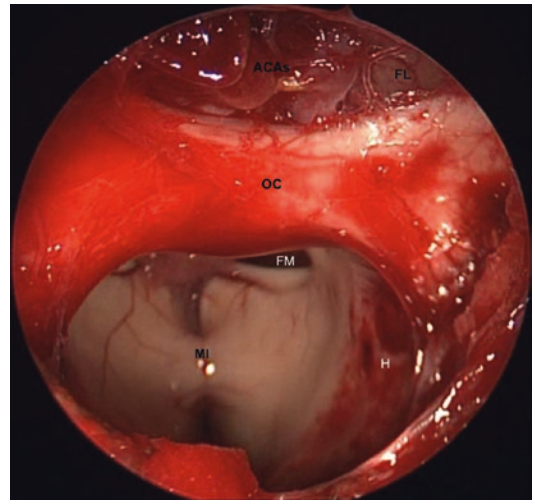

Fig. 22.7 The tumor has been removed and the interior of the third ventricle is seen. ACAs anterior cerebral arteries, FL frontal lobe, OC optic chiasm, FM foramen of Monro, MI massa intermedia (interthalamic adhesion), H hypothalamus (note raw appearance of the neural tissue after dissection from the tumor). (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

opened to the level of the planum. Sharp dissection along with debulking with an ultrasonic aspirator is used to separate the tumor from the optic apparatus, surrounding vessels, stalk, and third ventricle (Figs. 22.6 and 22.7).

In very large tumors that reach the third ventricle, angled endoscopes are used to inspect the interior of the third ventricle to look for residual tumor and possible obstructions to the CSF circulation (Figs. 22.8 and 22.9).

Closure techniques are tailored to the size of the defect created in the skull base and the integrity of the diaphragm. If the diaphragm is preserved, then the sella can be packed with fat, and a synthetic polymer plate is used as a strut to contain the graft in the sella. If the defect is very large or the CSF fistula observed in surgery is high flow, a vascularized nasoseptal flap can be developed and placed over the defect to facilitate healing.

In cases where the diaphragm is violated and there is communication with the third ventricle, fat packing should not be used as there is risk of migration into the ventricular system resulting in

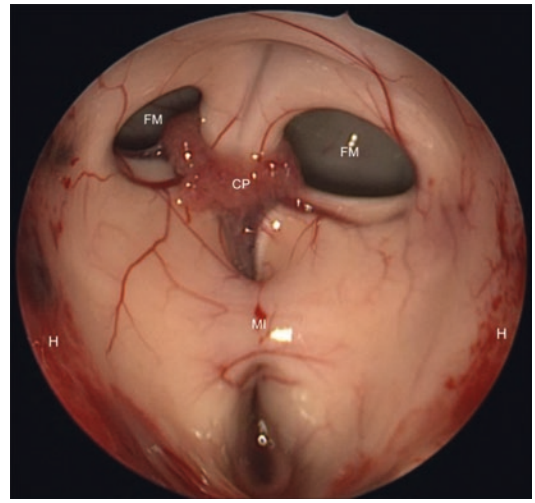

Fig. 22.8 View of the roof of the third ventricle with a 30-degree endoscope. FM foramen of Monro, CP choroid plexus, MI massa intermedia (interthalamic adhesion), H hypothalamus (note raw appearance of the neural tissue after dissection from the tumor). (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

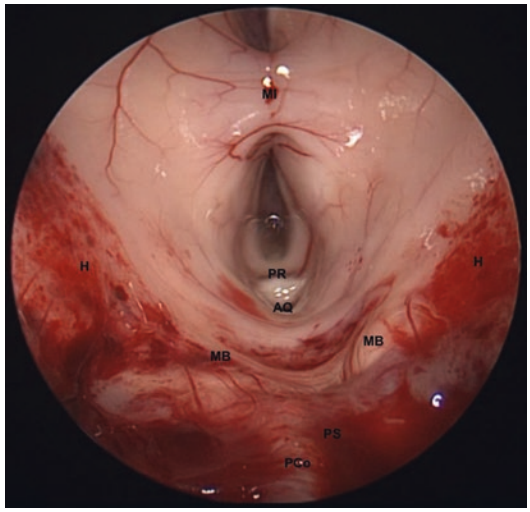

Fig. 22.9 View of the posterior third ventricle. Note the raw appearance of the third ventricular walls, corresponding to the hypothalamus (H). The pituitary stalk (PS) has been reduced to a very thin layer, through which the right posterior communicating artery (PCo) can be seen. MI massa intermedia, PR pineal recess, AQ cerebral aqueduct, MB mammillary bodies. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

ventriculitis or obstruction. In these cases, our preferred closure method is the gasket seal [143].

A fascia lata graft is harvested (synthetic materials can be used as well). A polymer plate is fashioned to match the size of the defect. Then the fascial graft is trimmed to be about 30% larger than the plate. The plate is countersunk over the fascia creating a "gasket" closure. The nasoseptal flap is then placed over the sealed defect. In these cases, a lumbar drain is usually placed and kept open to drain 5–10 ml/h for 48–72 h.

At the end of the procedure, the nasal passages are cleaned from debris, and the turbinates are returned to their position. Minimal packing is used, usually with hemostatic resorbable materials.

Improvement in endoscopic techniques with the use of extended approaches and angled endoscopes and instruments has allowed for transnasal resection of tumors that previously could only be reached transcranially. In experienced hands, the vast majority of pituitary adenomas can be now removed endoscopically regardless of the degree of suprasellar component. Limitations to this approach include lateral extension which cannot be reached from midline approach, extensive cavernous sinus involvement not accessible endoscopically, and tumors that encase blood vessels, especially if they are fibrous in nature.

Craniopharyngiomas represent a good example of how endoscopic techniques have proven an advantage over the transcranial approach. Extended endoscopic skull base approaches have allowed for improved extent of resection of these tumors with lower morbidity. The transsphenoidal approach allows for the tumor to be removed from its inferior portion, following its pattern of growth and allowing dissection from the optic apparatus and hypothalamus under direct visualization, rather than blind dissection from above typically done with the transcranial approach.

Special Neurosurgical Considerations Regarding Hypothalamic Injury

Preoperative Considerations

Based on magnetic resonance imaging (MRI), hypothalamic involvement can be evaluated based on the degree of involvement [144] (Figs. 22.10 and 22.11). In the case of craniopharyngioma, which is the tumor with the highest incidence of surgery-related hypothalamic injury, several classifications have been created in order to predict outcomes and to tailor the extent of resection in order to minimize injury. In the Müller classification, Grade 0 demonstrates no hypothalamic involvement. Grade 1 involves the anterior hypothalamus not involving mammillary bodies and hypothalamic areas hypothalamic areas hypothalamic areas beyond mammillary bodies, and Grade 2 involves both anterior and posterior hypothalamic areas including mammillary bodies and hypothalamic areas areas beyond mammillary bodies [144]. The grade of hypothalamic involvement has been shown to be associated with postoperative increase in BMI and a decrease in quality of life for these patients with craniopharyngioma [144]. For these reasons, for those with Grade 2 hypothalamic involvement in the setting of child-

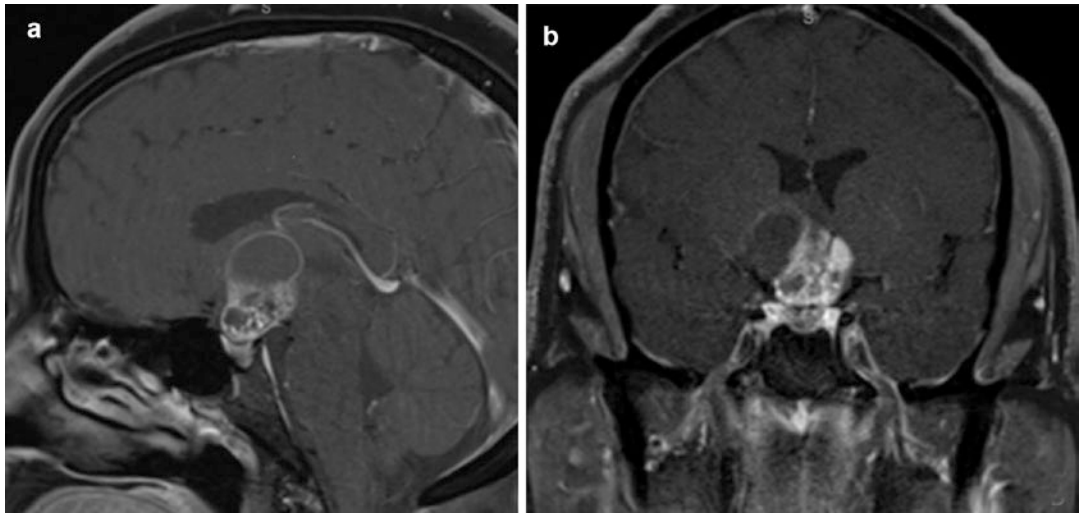

Fig. 22.10 Preoperative MRI T1 with contrast sagittal (**a**) and coronal (**b**) showing the craniopharyngioma growing in the suprasellar region into the third ventricle. Note the normal pituitary and normal size of the sella. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

Fig. 22.11 Preoperative axial non-contrasted CT showing the heavy calcification of this craniopharyngioma. (Courtesy of Roberto Rey Dios, MD, University of Mississippi Medical Center, Jackson, MS)

hood craniopharyngioma, Müller et al. discouraged radical excision surgery [144, 145]. Mortini et al. [146] found that in addition to the Müller classification of mammillary body involvement, other MRI findings can predict outcomes. Hypothalamic hyperintensity, unidentifiable pituitary stalk, dislocated chiasm, visibility of infundibular recess, ability to recognize the supraoptic recess, and retrochiasmatic tumor extension are associated with the development of postoperative obesity. Peritumoral edema, unidentifiable hypothalamus, hypothalamic compression, and fornix displacement in addition to inability to recognize the supraoptic recess were associated with postsurgical hypothalamic syndrome [146].

Mechanisms of Hypothalamic Injury

Injury to the hypothalamus, infundibulum, and pituitary stalk during surgery can happen through direct or indirect mechanisms. Direct injury is most often a result of accidental resection of hypothalamic tissue adherent to the tumor. This is more likely to occur when tumor dissection is done with suboptimal visualization, leading to traction and tearing of the neural tissue. This tends to happen more often in transcranial approaches for adherent tumors such as craniopharyngioma or dermoid cysts. Transsphenoidal resection of pituitary adenomas is usually done in an intracapsular fashion, without violating the diaphragm and arachnoid, thus resulting in lower risk of neural tissue injury.

Another mechanism of injury is ischemia secondary to vascular injury, vasospasm, or edema. The hypothalamus receives its blood supply from anteromedial branches of the anterior cerebral artery, the posteromedial branches of the posterior communicating artery, and the thalamoperforating branches of the posterior cerebral artery. Venous drainage occurs via the intercavernous sinuses [147].

In tumors requiring extracapsular dissection, avulsion of perforators can lead to immediate ischemia and death of the neural tissue. Ischemia can also occur in a delayed fashion as a result of vasospasm of these tiny perforators in the postoperative period. Severe edema after tumor resection can be seen, for example, when residual tumor is left behind. Arterial supply to the remaining tumor is compromised due to devascularization and venous drainage impaired after surgical manipulation. The result is tumor infarction, often with hemorrhagic transformation (i.e., pituitary tumor apoplexy) resulting in tumor swelling and compression of adjacent structures. The combination of venous congestion in the hypothalamic outflow and inflammatory response from the blood products results in edema, vasospasm, and ischemia of the neural tissue and subsequent hypothalamic injury. This is usually seen within 24–48 h after surgery [148].

Procedure-Related Iatrogenic Hypothalamic Injuries

Radiation Therapy

Radiation therapy (RT) is frequently used in the treatment of tumors of the suprasellar region, either directed to residual/recurrent tumors or as single modality treatment for tumors that cannot be surgically resected [149–152]. Modalities of RT include conventional external beam fractionated radiation therapy (usually delivered in a conformal fashion via intensity-modulated radiation therapy (IMRT)) and stereotactic radiosurgery, which involves higher doses in one to five fractions with a much more precise delivery system.

The goal of the treatment plan is maximum impact on tumor tissue with minimum impact on "normal" adjacent structures, including the hypothalamus [152]. Complications from RT can occur acutely (within days), early (within weeks), or late (months to years) [152]. Hypothalamic dysfunction can occur early [152]. Hypothalamic syndrome includes obesity or cachexia, impaired thermoregulation, and disturbances of the sleep/wake cycle [152, 144]. Adequate choice of RT modality, optimization of the conformality of the plan, shielding of critical structures, and adequate dose prescription and distribution can prevent such complications.

Deep Brain Stimulation

Deep brain stimulation (DBS) surgery has also been shown to result in iatrogenic hypothalamic injury. DBS surgery is primarily indicated to treat movement disorders, such as essential tremor and Parkinson's disease, eating disorders, behavior disorders, and pain syndromes [153]. Significant weight gain has been observed in patients with Parkinson's disease treated with deep brain stimulation using subthalamic implants (DBS-STN) up to 20 kg [154] which have been attributed to a decrease in energy expenditure [155–157]. However, disruption of the hypothalamic centers in charge of energy regulation has not been excluded [154]. Animal studies have implicated DBS of ventromedial hypothalamic nucleus as causing decreased HPA axis function via induction of a systemic inflammatory response [158].

Special Considerations in Neurosurgical-Associated Hypothalamic Dysfunction Manifestations

Central Diabetes Insipidus (CDI)

In central DI, damage to the magnocellular neurons of the supraoptic and paraventricular hypothalamic nuclei results in inadequate production of arginine vasopressin (AVP) or antidiuretic hormone (ADH) to be able to release into the bloodstream by the posterior pituitary [159]. The primary clinical manifestation includes hypotonic polyuria with compensatory polydipsia and may occur as a complication of pituitary surgery

in up to 31% of cases [159–161]. Postoperative DI can follow one of the three courses: transient, permanent, and triphasic. Transient CDI, the most common type of CDI pattern, postoperatively occurs due to dysfunction of magnocellular neurons after surgical manipulation and may occur abruptly within 24–48 h and may last up to 5–10 days [159, 161]. Rarely, 80–90% of AVP-secreting neurons are damaged, and permanent DI may occur [160]. The third possible course is a triple-phase response [161]. The first phase, which is identical clinically to transient DI, begins within 24 h of surgery and typically lasts 4–5 days. This occurs because of absent or decreased ADH release from hypothalamic neuronal shock. Following this initial response, an interphase occurs beginning around 1 week postoperatively and lasts for approximately 1 week. As injured hypothalamic magnocellular neurons degenerate, they release their remaining ADH stores leading to water retention and decreased urine output. In some patients, hyponatremia may develop. This interphase is followed by the final phase whereby permanent DI ensues due to complete degeneration of neurons in the supraoptic and paraventricular hypothalamic nuclei [160, 162–164]. It is very rare, and only 1–3% of patients develop this triphasic response postoperatively from hypothalamic injury.

Hypothalamic Obesity Syndrome with Hyperphagia

HOS is characterized by a rapid, unrelenting weight gain that may be accompanied by severe hyperphagia due to hypothalamic damage or injury and in association with other hormonal imbalance attributed to the hypothalamic-pituitary function [154]. The pathophysiology is based around many key nuclei within the hypothalamus. Investigators found that lesions to the hypothalamic ventromedial area, paraventricular nucleus, or dorsal medial hypothalamic nuclei produced hyperphagia and obesity in rats, whereas lesions of the lateral hypothalamus resulted in hypophagia [154]. These findings gave rise to the hypothesis that the ventromedial area and the lateral hypothalamus can be categorized as the satiety and hunger centers, respectively [154]. The arcuate nucleus located in the base of the hypothalamus primarily hosts the neurons expressing proopiomelanocortin (POMC) and neuropeptide-Y (NPY) [154]. POMC inhibits feeding and increases energy expenditure, whereas NPY stimulates feeding and decreases energy expenditure [154]. Both of the hormones leptin and insulin increase the expression of POMC and decrease the expression of NPY [154]. Preoperatively, imaging findings showing tumor and hypothalamic involvement have been found to be associated with postoperative obesity [145, 146]. This syndrome has been reported to potentially be associated with deep brain stimulation as well [154].

Sympathetic Dysfunction

In a case series, refractory hypotension as a manifestation of hypothalamic injury postoperatively can occur in approximately 1.5% [165]. Systemic hemodynamic response has been attributed to the paraventricular nuclei and zone AV_3V of the hypothalamus [165–169]. Although very uncommon, neurosurgeons should be aware of this phenomenon that can occur after sellar tumor surgery and be prepared to act quickly with sympathomimetic drugs [165].

Acquired Central Hypoventilation

"Acquired central hypoventilation" is exceedingly rare, and there are very few reports of this from injury to neurological structures after surgery. One case report presented a 15-year-old female who underwent a right-sided pterional craniotomy for resection of craniopharyngioma [170]. She had her first surgery complicated by permanent DI. She presented 2 months after with worsening vision and recurrence of the cystic component of the craniopharyngioma. An orbitopterional approach craniotomy was performed; however, the evening after the surgery, an attempted extubation failed even with the patient being awake and following commands. Ventilatory failure persisted until postoperative day 14. The cause of central hypoventilation in this mentioned case report was attributed to hypothalamic dysfunction. Diagnostics done included endocrinological testing, liver function

tests, chest radiographs, and repeat MRI as this was a diagnosis of exclusion. The paraventricular nucleus of the hypothalamus has been previously studied to project to medullary and spinal cord respiratory centers [170]. Leptin, a hormone produced by the adipose tissues and that acts on hypothalamic receptors, has been implicated to hypoventilation as well [170, 171].

Intraoperative Hyperthermia

A case report described an intraoperative occurrence of intraoperative hyperthermia to 40.1 °C within 20 min as the surgery for craniopharyngioma excision was ending [172]. There was no noted deviation from their standard induction or maintenance anesthetic. They managed the patient as malignant hyperthermia and discontinued inhalational anesthetic and administered paracetamol, propofol, and intravenous cold saline. Hypernatremia and an increase in urine output to 25 mL/kg/hour were noted, and DI was suspected. Diagnostic workup for possible causes was done including infection, neuroleptic malignant syndrome, thyroid dysfunction, or transfusion reaction. Due to the temporal association of the resection and tumor manipulation with the hyperthermia, this event was attributed to hypothalamic affectation [172]. Anticipation of this potentially lethal complication should be in every surgical planning.

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