Introduction

Hormonal signaling systems are critical to basic homeostatic functions. They support the control of volume status, blood pressure, cellular metabolism, and intracellular signaling. The hypothalamic–pituitary–adrenal (HPA) axis, in particular, comprises systems to regulate sodium and water balance, steroid hormone production, glucose metabolism, and thyroid function. Each hormonal system is controlled via negative and positive feedback loops. In addition, activity levels are affected by intersystem modulation. These feedback mechanisms, with the goal of immediate homeostasis, often cloud hormonal measurement and diagnosis in the critically ill patient. Any kind of intracranial pathology and, in particular, traumatic brain injury (TBI), stroke, or cerebral hemorrhage disequilibrate the HPA axis. This frequently results in deleterious clinical sequelae. In addition, endocrine disorders unrelated to neuropathology have significant impact on neurophysiology. Thus, dysfunction of the HPA axis must be recognized and carefully managed during the perioperative period.
Overview

**Sodium and Water Balance**

The extracellular fluid volume reflects total body sodium. Under healthy physiologic conditions, the plasma sodium concentration reflects total body water. The plasma osmolality is sensed by the hypothalamus and tightly regulated. Abnormalities of serum Na⁺ are common in the neurosurgical and neurotrauma setting. Hypo- or hypernatremia frequently stems from aggressive perioperative volume resuscitation (e.g., following trauma, hemorrhage, or in the context of cerebral vasospasm). Dysfunction of the hypothalamus, pituitary, or adrenal glands is a common secondary cause for sodium or water imbalance.

**Antidiuretic Hormone (Arginine Vasopressin, Desmopressin [Synthetic])**

Antidiuretic hormone (ADH) is produced in the hypothalamus, and it is stored and secreted by the posterior pituitary in response to (1) increased plasma osmolality as detected in the hypothalamus; (2) decreased plasma volume as detected by peripheral and central baroreceptors; (3) general stress, pain, or increased ICP; and (4) a decrease in plasma angiotensin.

Circulating ADH induces an increase in free water absorption in renal collecting ducts (receptor: V2 GPCR), release of CRH/ACTH (receptor: V1b GPCR in hypothalamus), blood pressure (receptor: V1a), and release of atrial natriuretic peptide (ANP).

**Natriuretic Peptides**

Natriuretic peptides [e.g., ANP, BNP, C-type natriuretic peptide (CNP)] are released by the cardiac atria and by the hypothalamus in response to increased intravascular volume (atrial wall tension) and increased ICP. Natriuretic peptides increase renal sodium excretion and vascular permeability. Natriuretic peptides also antagonize ADH effects as well as angiotensin II effects. Natriuretic peptides, *produced in the brain*, modulate systemic effects of circulating ANP (which does not cross the blood–brain barrier) via receptors in the hypothalamus (e.g., decrease H₂O and salt appetite), and they decrease sympathetic tone via actions on the brainstem. Brain ANP can effect localized increases in cerebral blood flow and decreased CSF production and is actively transported out of the brain across the blood brain barrier. Plasma BNP levels may increase as a result of subrachnoid hemorrhage and contribute to hypovolemia and be a marker of associated cardiac dysfunction. (Taub
Elevated BNP levels may be associated with cerebral ischemia from multiple etiologies, including vasospasm, after SAH. Overall, little is known about the role and the clinical significance of CNP.

**Implications for the Neurosurgical Patient**

**Sodium and Water Balance**

Derangements of water and sodium in the neurosurgical population, especially acute changes, are concerning for possible clinical sequelae that include: cerebral edema, altered mental status, seizure, or coma, increased ICP, cerebral hypoperfusion, cerebral vasospasm, and bridging vein rupture with associated subdural hemorrhage.

Frequently, the clinician is alerted by an abnormal serum sodium concentration, which triggers a thorough workup. Complete evaluation must take into consideration the multiple causes of altered serum sodium concentrations, and these must be evaluated in the final differential diagnosis.

**Hyponatremia (<135 mEq/L)**

A lower than normal serum sodium concentration reflects excess of free water (fluid overload) or an improper sodium loss. Clinical symptoms usually manifest with an acute drop of serum sodium concentration to lower than 125 mEq/L and include muscle weakness, cerebral edema, lethargy, confusion, seizures, and coma. Hyponatremia that develops over many days and continues chronically can be tolerated for quite some time without major signs or symptoms. The main hormonal mediators leading to hyponatremia are ADH (classical symptom complex called syndrome of inappropriate ADH release: SIADH) and ANP (atrial natriuretic protein; causing increased natriuresis). The differential diagnosis of hyponatremia includes SIADH, cerebral salt wasting syndrome (CSW) and dilutional state (volume overload and hyperprotein state). Hyponatremia is also found with Addison’s disease because of reduced production of aldosterone, an adrenal hormone that acts to increase reabsorption of sodium in the kidney tubules. Ultimately, a careful assessment of the fluid/volume status will guide diagnosis and management. The total sodium deficit may be estimated via the formula: $0.5–0.6 \times (\text{wt. in kg}) \times (\text{goal-measured Na}^+)$. 

<table>
<thead>
<tr>
<th>Table 2.1 Diagnostic criteria for SIADH</th>
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<tbody>
<tr>
<td>• Volume status? euvolemia or mild hypervolemia</td>
</tr>
<tr>
<td>• Urine output? low urine output (as low as 500 mL/d)</td>
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<tr>
<td>• Urine osmolality? concentrated urine (&gt;800 mOsm/L)</td>
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<tr>
<td>• Plasma osmolality? ↓plasma osmolality (us. &lt;280 mOsm/L) ↓Na⁺</td>
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<tr>
<td>• Consider or exclude CSW (see below and table)</td>
</tr>
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**Table 2.2  Treatment of SIADH**

- Goal to correct Na⁺ levels gradually
- Normal saline with free water restriction usually adequate
- Loop diuretics (cause net free water loss)
- Correct deficit gradually
  - 10 mEq/L over 24 h; or 1–2 mEq/L in first hour in symptomatic patients
  - 3% Hypertonic saline to correct severe Na⁺ deficit
- Tolvaptan (SamscaR) - renal ADH receptor antagonist (15mg-60mg PO daily)
- Demeclocycline (1–2 mg PO/d) blocks renal action of ADH
  - Side-effect profile similar to tetracyclines
  - May be nephrotoxic

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**Syndrome of Inappropriate Secretion of ADH**

SIADH is an umbrella classification for the clinical presentation of hyponatremia with euvolemia or mild hypervolemia (Table 2.1). SIADH is a common diagnosis after TBI, brain surgery, and in association with intrinsic neuropathology. In addition, there are many other confounding etiologies. The hallmark laboratory finding of SIADH is a continued secretion of ADH despite decreased plasma osmolality. However, elevated serum ADH concentration is not specific for SIADH. Elevated ADH levels have also been reported in the context of opioid treatment, general anesthesia, perioperative stress response, brain tumors, and CSW. ADH levels are also increased in the treatment phase of DI.

Treatment of hyponatremia must be accomplished gradually (Table 2.2), as too rapid correction may result in permanent structural injury in the brainstem (e.g., central pontine myelinolysis). In addition, hyperchloremic metabolic acidosis is a common finding when the primary treatment for hyponatremia involves administration of saline. To avoid this concern, many clinicians administer sodium as a mixture of chloride and acetate salts.

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**Cerebral Salt Wasting Syndrome**

CSW is a diagnosis of exclusion that presents as hyponatremia (secondary to renal sodium loss) with hypovolemia and maintained or elevated urine output. Unfortunately, there is no simple assessment method available to determine the intravascular volume status of a patient. The central venous pressure (CVP) may be useful for a trend. Serial cardiac echo examinations also help to assess intravascular volume, but require significant expertise and are expensive to perform. Systolic pressure variation (SPV) as measured by the pulse oximetry plethysmograph or arterial line wave form is helpful to assess volume status in patients receiving positive pressure ventilation. CSW may be particularly common in subarachnoid hemorrhage. Likely, CSW develops secondary to the derangement of neurohumeral signals which results in increased ANP levels and decreased renal sympathetic input (Tables 2.3 and 2.4).
Hypernatremia (>145 mEq/L)

Severe elevation of Na+ serum levels (>160 mEq/L) is associated with increased mortality in neuro ICU patients. Symptoms include change in mental status, seizures, myoclonus/hyperreflexia, and nystagmus. Acute hypernatremia may also result in structural, permanent injury in the brainstem (e.g., central pontine myelinolysis). In addition, patients may show signs of intravascular volume depletion, cerebral hypoperfusion, and/or cerebral vasospasm. Intravascular hypernatremia will cause water to move from brain cells, resulting in decreased brain volume, which carries the risk of disruption of bridging veins and subsequent subdural hematoma. Hypernatremia can be caused by central or nephogenic diabetes insipidus (DI) or can be iatrogenic, secondary to aggressive saline infusion. Less likely, it develops with overly aggressive diuresis. Hypernatremia can also be seen with mineralocorticoid excess, as is observed with Conn’s syndrome or Cushing’s syndrome (accompanied by a reduction in serum potassium levels). It is important to differentiate between central DI and nephogenic DI. Central DI is caused by an interruption of hypothalamic signaling (anatomic and ischemic), with subsequent reduction in ADH secretion from the posterior pituitary (e.g., after TBI, tumor resection, vasospasm of anterior circulation, brain death). Nephrogenic DI is characterized by lack of renal response to serum ADH associated with critical illness, antibiotics, contrast, or renal insult.

Common symptoms for both central and nephogenic DI are hypernatremia, hyperosmolality, and dilute polyuria. Central DI presents with severely reduced urine osmolality: <200 mOsm/L versus 200–500 mOsm/L with nephrogenic DI. Table 2.5 lists diagnostic criteria for DI, and Table 2.6 list strategies for initial management of DI.
The use of diuretic and osmotic agents or hypervolemic therapy with saline will invariably complicate the clinical assessment of sodium derangements. A careful assessment of overall volume status is critical in determining diagnosis and treatment plan. For example, treatment should be fluid replacement in patients who have water deficit versus fluid restriction in patients thought to have SIADH, while fluid and sodium administration would be the best treatment for patients with CSW. In contrast, volume restriction in a patient with CSW, for example, would further worsen volume deficit and hyponatremia, especially in the context of vasospasm and impending cerebral ischemia following subarachnoid hemorrhage. Also, aggressive treatment of hyponatremia can lead to over-correction (i.e., hypernatremia) and an associated demyelination syndrome, while aggressive treatment of hypernatremia may result in cerebral edema due to organic intracerebral osmolytes that exist in brain.
Neuroendocrine Physiology: Fundamentals and Common Syndromes

Overview

Steroid Hormone Physiology

Cortisol is the primary glucocorticoid hormone of clinical relevance. It is secreted by the zona fasciculata of the adrenal gland in response to adrenocorticotropic hormone (ACTH). ACTH, in turn, is secreted by the pituitary in response to corticotropin-releasing hormone (CRH) produced by the hypothalamus. Cortisol is key to the regulation of energy metabolism, electrolyte homeostasis, and immune function. It interacts with nuclear receptors found throughout the body including the brain. The secretion of cortisol is tightly regulated along the HPA axis. Dysregulation at any point of the HPA axis will result in excess or deficiency of cortisol with marked clinical consequences. The basal daily cortisol requirement ranges between 15 and 25 mg hydrocortisone (8 mg/m²/d; conversions: prednisone = 0.25 × hydrocortisone; dexamethasone = 0.04 × hydrocortisone). Cortisol production is subject to diurnal variation as well as modulation from a host of physiologic factors. Measurement of random cortisol levels is rarely useful in clin-

Key Points

Sodium and Water Balance (Table 2.7)

- Always consider Na⁺ abnormality in setting of pituitary tumor/intracranial surgery, hypothalamic injury, TBI, seizure, treatment for cerebral vasospasm/stroke, or acute/chronic change in mental status.
- Na⁺ derangements may simply be related to fluid management (e.g., hypervolemic therapy, hypertonic saline, diuretics, or normal saline with stress-elevated ADH).
- Clinical picture more helpful than diagnostic testing in diagnosis.
- Other endocrine disease (adrenal, thyroid) must be considered.
- If increased Na⁺ consider DI or over-resuscitation with saline.
- If decreased Na⁺ consider SIADH or CSW.
- Correct abnormalities gradually with frequent measurement and monitoring.

<table>
<thead>
<tr>
<th>Table 2.7 Features of Common Na⁺ derangements</th>
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<tr>
<td>Central DI</td>
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<tr>
<td>Serum Na⁺ &gt;145 mEq/L</td>
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<tr>
<td>PE suggests hypovolemia</td>
</tr>
<tr>
<td>↑Na⁺ with saline admin</td>
</tr>
<tr>
<td>1° Defect in water handling</td>
</tr>
<tr>
<td>↑Serum osmolality</td>
</tr>
<tr>
<td>Low urine Osm</td>
</tr>
<tr>
<td>IV Desmopressin</td>
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<tr>
<td>Oral salt tablets</td>
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</table>
ical assessment of the HPA axis although AM cortisol levels may be useful in conjunction with other tests and the clinical presentation. It should be noted that although dexamethasone is a commonly prescribed steroid in clinical medicine, it has no mineralocorticoid activity. In addition, it is important to recognize that cortisol requirements increase as much as five times basal requirements under physiologic stress (e.g., infection, shock, and surgery). Inadequate steroid administration during stress will result in hemodynamic instability (primarily hypotension), hypoglycemia, hyponatremia and hyperkalemia. However, for most surgeries, “stress-dosing” of steroids for patients on chronic steroid supplementation is no longer routine. Stress steroid dosing is not based on strong supportive evidence. Current evidence supports maintenance dosing (i.e. the usual daily dose) on the day of surgery with additional intravenous supplementation with hydrocortisone supplementation, if overt hypotension presents in the perio-operative period. Laboratory testing using cortisol levels or ACTH stimulation tests does not appear to be helpful in the majority of patients.

Aldosterone is the primary mineralocorticoid of clinical concern. Mineralocorticoid activity is central to the maintenance of effective plasma volume via the renin–angiotensin–aldosterone axis. Aldosterone is secreted by the adrenal cortex in response to many physiologic events (e.g., hypotension, hypovolemia, and acidosis), in response to the production of ACTH, and in response to release of adrenoglomerulotropin from the pineal gland. Aldosterone acts to promote sodium and water reuptake and potassium secretion from the glomerulo-filtrate in the kidney. In addition, CNS aldosterone receptors contribute to the modulation of fluid balance. Fludrocortisone (Fluorinef) is the only available therapeutic drug that approximates the aldosterone activity.

### Adrenal Insufficiency

Frequently, patients with adrenal insufficiency remain free of clinical signs and symptoms during normal daily activities. Those who develop a chronic disease develop nonspecific symptoms such as lethargy, muscle weakness, dizziness, syncope, and diarrhea or constipation. However, adrenal insufficiency may present as acute crisis secondary to infection, physiologic stress (trauma and major surgery), or abrupt withdrawal of steroid supplementation. Adrenal insufficiency should always be considered in the setting of refractory hypotension/shock. Pathophysiology of primary adrenal insufficiency is described in Table 2.8.

<table>
<thead>
<tr>
<th>Table 2.8 Pathophysiology of primary adrenal insufficiency (Addison’s disease)</th>
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<tbody>
<tr>
<td>• Absence of glucocorticoid and mineralocorticoid function</td>
</tr>
<tr>
<td>• ↓[Na+]p, ↑[K+]p (absent aldosterone effects)</td>
</tr>
<tr>
<td>• Primary clinical issue: hypotension/hypovolemia/shock</td>
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<tr>
<td>• May lead to cerebral hypoperfusion and cerebral ischemia</td>
</tr>
<tr>
<td>• Diagnose by total plasma cortisol levels and CRH levels</td>
</tr>
<tr>
<td>• Hyperpigmentation 2° ↑ pituitary secretion of ACTH precursor → ↑α-MSH</td>
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- Absence of glucocorticoid and mineralocorticoid function
- ↓[Na+]p, ↑[K+]p (absent aldosterone effects)
- Primary clinical issue: hypotension/hypovolemia/shock
- May lead to cerebral hypoperfusion and cerebral ischemia
- Diagnose by total plasma cortisol levels and CRH levels
- Hyperpigmentation 2° ↑ pituitary secretion of ACTH precursor → ↑α-MSH
Addison’s Disease

Primary adrenal insufficiency is commonly caused by autoimmune or infectious processes, cancer, adrenal infarction, or adrenalectomy. It is associated with inadequate production of both glucocorticoid and mineralocorticoid hormones, which then require pharmacologic replacement (e.g., hydrocortisone and fludrocortisone).

Secondary Adrenal Insufficiency

If adrenal insufficiency develops in the absence of intrinsic adrenal pathology, the symptom complex is called “secondary adrenal insufficiency.” A multitude of causes can lead to secondary adrenal insufficiency and are summarized in Table 2.9. Tables 2.10 and 2.11 describe diagnostic criteria and treatment options for adrenal insufficiency, respectively.
Cushing’s Disease and Syndrome

Cushing’s syndrome results from an overproduction of ACTH in the pituitary, which results in overproduction of cortisol by adrenal glands (Cushing’s disease). Excess cortisol can also be due to primary overproduction in the adrenal glands or from overproduction of ACTH by paraneoplastic tissue (observed in patients with small cell lung cancer) (Table 2.12). Most commonly, the Cushing’s-like syndrome is due to excessive glucocorticoid administration in the treatment of edema surrounding brain tumors, asthma, arthritis, or for immune suppression in the setting of organ transplantation. The syndrome is characterized by hyperglycemia, insulin resistance, and metabolic syndrome; blood pressure elevation, central obesity, and dyslipidemia.

Table 2.11  Treatment of adrenal insufficiency

- Treat empirically in cases of high clinical suspicion
- Hydrocortisone 150–300 mg IV per day approximates a physiologic stress dose
- Supplemental steroids must be tapered to avoid recrudescence
- Fludrocortisone (0.05–0.2 mg/d) provides mineralocorticoid replacement
  - Only necessary in Addison’s management
  - Hydrocortisone (20 mg) approximates 0.05 mg fludrocortisone
- Assess for cause of acute insufficiency

Table 2.12  Causes, diagnosis, and treatment of Cushing’s syndrome/disease

**Causes**

- Cushing’s disease: primary pituitary overproduction of ACTH
- Cushing’s syndrome: associated with increase in cortisol from other origin other than pituitary ACTH excess
- Exogenous corticosteroids (e.g., treatment for perifocal brain edema, autoimmune disease, Addison’s disease)
- Oversecretion of cortisol in adrenal glands OR primary ACTH secreting tumor (e.g., small-cell lung cancer)

**Diagnosis**

- Plasma cortisol and ACTH levels
- Urine cortisol levels
- Dexamethasone suppression test
- Pituitary imaging (MRI) and petrosal ACTH sampling

**Treatment**

- Surgery, pulse radiotherapy, and medical pharmacotherapy with dopamine agonists (bromocriptine) and direct cortisol synthesis inhibitors (ketoconazole, metyrapone)
Implications for the Neurosurgical Patient

Steroid Hormone Derangements

Increased plasma cortisol levels (e.g., with Cushing’s disease, exogenous steroid therapy) are associated with significant clinical problems. For example, patients are likely to develop a metabolic syndrome with glucose intolerance. Excessively increased blood glucose levels are associated with increased morbidity after TBI and stroke, increased diuresis followed potentially by hypovolemia and systemic hypotension. Hyperglycemia is also associated with increased infection risk.

Patients with Cushing’s disease may present with mass effect in their brain, if associated with enlarging pituitary adenoma. Overall, patients with elevated cortisol may present with hypertension (intravascular volume excess), obesity, and difficulty with venous access or airway management, impaired cognition, memory, and muscle strength, which may confuse neurologic assessment. Therapeutic application of exogenous steroids should be guided by great caution. Some patients treated with exogenous hydrocortisone may, in fact, show an enhanced response to vasopressors/catecholamines, which can be used favorably in the context of circulatory compromise or shock.

Decreased plasma cortisol levels (e.g., with Addison’s disease or secondary adrenal insufficiency) expose the critically ill neurosurgical patient to the risk of severe complications. These include: (1) systemic hypotension with decreased CPP, (2) hyponatremia with associated effects (see above section), (3) decreased mental status, (4) hypoglycemia, (5) fever with increased cerebral metabolic rate, and (6) diminished response to catecholamines/vasopressors.

Concerns and Risks

Of particular concern in the neurocritical care patient population are missed diagnosis of adrenal insufficiency, inadequate supplementation of steroids in the perioperative period and uncontrolled hyperglycemia associated with increased plasma cortisol levels from endogenous or exogenous sources. The use of etomidate for induction or sedation of anesthesia is a risk factor for secondary adrenal insufficiency in patients with poor physiologic reserve.
Overview

Thyroid Hormone

Thyroid hormone is produced by thyroid gland in response to thyroid stimulating hormone (TSH) released by the anterior pituitary and thyroid releasing hormone (TRH) in the hypothalamus. Thyroid hormone is present in the serum as T3, T4, and rT3, where free (not protein bound) T3 is the active form of the hormone. Levels of free T3 are dependent on a variety of factors, including protein binding that can be dramatically impacted by critical illness. Careful analysis of the clinical presentation with an emphasis on specific syndromes and thyroid ultrasonography are useful in diagnosis. Disruption of thyroid hormone levels lead either to hypothyroidism (not enough T3) or hyperthyroidism (excess T3). Tables 2.13 and 2.14 summarize the pathophysiologic characteristics of the two states. Table 2.15 lists the therapeutic interventions in case of a hyperthyroid crisis (“thyroid storm”). Table 2.16 summarizes the implications for the neurosurgical patient.

Table 2.13  Pathophysiology of hypothyroidism

| • Primary hypothyroidism                  |
| o Decreased production of thyroid hormone by the thyroid gland |
| o Commonly subclinical                    |
| o Often associated with adrenocortical insufficiency |
| o Laboratory studies typically indicate elevated TSH (>4 mIU/mL) and low free T4 and total T3 |
| o Thyroid disease secondary to CNS pathology may present with ↓, nl. or ↑ TSH |
| o Laboratory values (esp. TSH) may be influenced by critical illness |

| • Secondary hypothyroidism            |
| o Associated with neurologic disease, particularly if the process involves the pituitary or hypothalamus |
|  ▪ ↓TSH or ↓TRH                       |
| o Also common during chronic treatment with amiodarone |


Key Points
Steroid Physiology

• Cortisol requirements significantly increase with physiologic stress
• Accurate assessment of adrenal axis in critical illness is very challenging
  – Normal levels may be misleading in diagnosis
  – Serum cortisol is highly protein bound
• Free (active) levels fluctuate with stress–response and critical illness
• Adrenal insufficiency should always be considered with shock in setting of critical illness
  – Benefits of empiric therapy may outweigh risks
Table 2.14  Pathophysiology of hyperthyroidism

- Elevated thyroid activity most commonly associated with
  - Graves’ disease due to the activation of the thyrotropin receptor by autoantibodies
  - Toxic adenoma/multinodular goiter
- Laboratory values: depressed TSH; elevated free T4 level
- TSH may be elevated in pituitary adenoma
- Acute thyrotoxicosis transforms into life-threatening thyroid storm during acute physiologic stress: anesthesia, surgery, trauma, infection, exogenous iodine bolus
- Thyroid storm presents with:
  - Hyperthermia (fever/sweating)
  - Increased carbon dioxide production/metabolic rate
  - Arrhythmia, especially atrial fibrillation
  - Seizure/coma
  - Severe hypertension advancing to CHF and shock

Table 2.15  Management of thyroid storm

1. Acetaminophen and active cooling if indicated
2. Beta-blockade for control of tachycardia (propanolol if no pulm contraindications)
3. Intravenous hydrocortisone (100–150 mg IV q8h)
4. Methimazole (rectal, oral, IV) or propythiouracil (PO, rectal)
5. Potassium or sodium iodide (4–6 drops PO q6h)

Table 2.16  Implications for the neurosurgical patient: Thyroid function

- **Hypothyroidism** (especially severe or late; rarely in subclinical)
  - Goiter with airway compromise (PE, symptomatology, CT)
    - ↑ tongue size can occur
  - Preoperative hypovolemia (induction hypotension)
  - Nonspecific ECG changes (esp. low voltage and T-waves)
    - May also evidence amyloid-related conduction abnormalities
  - Decreased gastric emptying (aspiration risks)
  - Impaired ventilatory response to hypoxia or hypercapnea
  - Weakness of accessory muscles (respiratory function)
  - Possible decreased hemostasis
  - Decreased BMR with hypothermia
  - Depressed myocardial contractility
  - Delayed emergence
  - Opioid sensitivity
  - Associated hypoglycemia, anemia, SIADH
  - Myxedema coma
    - Decreased mental status, hypothermia, non-pitting LE edema
    - Very elevated TSH, extremely low T3, T4
  - No effect on MAC of potent agents or nitrous oxide

- **Hyperthyroidism**
  - Goiter (as above)
  - Fever with increased cerebral metabolic rate
  - Hypercapnia with increased cerebral blood flow/volume
  - Cardiac arrhythmias – especially atrial fibrillation
  - Cardiomyopathy with clinical heart failure syndrome
  - Changed in mental status with seizures or coma in thyroid storm
  - Neurologic features: visual symptoms, muscle weakness, tremor
  - Possible hypercortisolism 2° to accelerated metabolism of steroids
  - Hyperglycemia
Concerns and Risks

Thyroid Function

Advanced hypothyroidism may manifest in the perioperative period with neurologic symptoms, respiratory failure, or delayed emergence that may confound postoperative assessment. Thus, hypothyroid patients presenting for surgery should be adequately treated with thyroid hormone if possible before their operation. Similarly, hyperthyroidism must be treated, if at all possible, prior to surgery, because malignant hyperthyroidism and the associated hypermetabolic state carries the risk for deleterious cardiovascular and neurologic complications during the perioperative period.

Key Points

Thyroid Function

- Thyroid dysfunction can be difficult to assess in setting of physiologic stress response and critical illness
- Clinical hyperthyroidism can advance to life-threatening thyrotoxicosis in the perioperative setting
  - Suppress hyperthyroid state prior to OR unless surgery is emergent
- Depressed thyroid function should be normalized before elective surgery

Overview

Additional Neuroendocrine Systems

Pheochromocytoma

Pheochromocytoma is a metabolically active neuroendocrine tumor of chromaffin cells commonly found in the adrenal glands, although these tumors can be found in other sites. A high suspicion of pheochromocytoma should be raised in neurosurgical patients with a history of neurofibromatosis type I, Von Hippel-Lindau disease, multiple endocrine neoplasia type II, and familial carotid body tumors. Routine screening is recommended prior to elective surgery in these patients and should also be given consideration for patients with severe hypertension of unknown etiology, especially in the 30–40 year age group. Presenting symptoms may also include headache, excessive truncal sweating, palpitations, or panic attacks. These tumors
secrete norepinephrine, and sometimes epinephrine, resulting in hemodynamic instability such as paroxysmal swings in blood pressure and, most frequently, severe hypertension. The release of catecholamines is triggered by physiologic stress or physical manipulation of the lesion.

The standard diagnostic tests are measurement of plasma-free metanephrines (high specificity) and 24-h urine metanephrines (high sensitivity). The clonidine suppression test is sometimes employed. Physiologic tests are complemented by sensitive imaging modalities, including MRI and scintigraphy.

The masses can go undiagnosed, then manifest as exaggerated autonomic responses during anesthesia for unrelated surgical procedures. In the untreated patient with pheochromocytoma, desensitization of beta-receptors may occur and be associated with decreased response to exogenously administered catecholamines. Significant volume depletion also occurs in the setting of chronically elevated sympathetic tone. As a result of these derangements, cardiovascular collapse may occur during induction and maintenance of general anesthesia.

In patients with known pheochromocytoma, preoperative antagonism of catecholamine effects (usually over weeks preceding surgery) is essential. Therapy should start with a peripheral alpha-1 antagonist such as phenoxybenzamine, followed by the addition of beta-antagonists. Beta-selective antagonists should not be administered before alpha blockade, as negative inotropy in the setting of unopposed alpha-receptor-mediated vasoconstriction can result in acute ventricular dysfunction. Furthermore, beta-blockade alone is contraindicated because it does not prevent and can actually augment effects of catecholamines at alpha-adrenoreceptors. Finally, the addition of the catecholamine synthesis inhibitor alpha-methyl-p-tyrosine (AMPT) 10–14 days prior to surgery is current standard of care, as it decreases the requirement for peripheral adrenergic blockade resulting in greatly improved perioperative hemodynamic stability. Preoperative volume repletion is clearly beneficial. Adequate preoperative preparation may be demonstrated by controlled hypertension, minimal orthostasis, and minimal ectopy on heart rhythm monitoring on the day of surgery.

Intraoperative management consists of IV infusion of titratable antihypertensives, which may include alpha- and beta-blockers as well as direct vasodilators. Administration of indirectly acting vasopressors, such as ephedrine, may have unpredictable effects and is best avoided. If the surgical plan includes tumor excision (or clamping of veins draining the mass), dramatic hypotension should be anticipated shortly thereafter due to the loss of catecholamines in a patient aggressively alpha-blocked. The plan for anesthesia should, therefore, include invasive arterial monitoring, with preparation for post-excision resuscitation, hemodynamic support, and cortisol supplementation (if adrenal).

**Growth Hormone/Acromegaly**

Growth hormone is secreted by the anterior pituitary gland and is a diffuse regulator of cellular metabolism. The hormone stimulates production of insulin-like growth
factor I, serum levels of which may be diagnostic for the disorder. Growth hormone excess, commonly due to a hyperactive pituitary macroadenoma, is common in neurosurgical patients presenting for pituitary surgery.

Acromegaly from growth hormone excess has important anesthetic considerations. These include: (1) potential for a difficult airway (including postoperative airway obstruction) due to diffuse soft-tissue enlargement, laryngeal calcification, recurrent laryngeal nerve involvement, and severe sleep apnea; (2) cardiac dysfunction including conduction abnormalities, cardiomyopathy, microvascular disease, and severe hypertension; (3) associated abnormalities of other hormones of the HPA axis with attendant derangements; (4) challenging intravenous access due to diffuse skin thickening; (5) and possible increase risk of positioning related nerve injury due to pre-existing nerve compression or entrapment in fascial compartments.

Frequently, surgical excision of a pituitary adenoma is performed via a transphenoidal approach under general endotracheal anesthesia. Special attention is necessary in airway management. This includes consideration regarding the impact of anesthetic agents (esp. benzodiazepines and opioids) on postoperative respiratory function. Preoperative cardiac assessment including ECG and echocardiography should be strongly considered. Electrolytes should also be checked prior to surgery and serially after resection in the intensive care unit (see diabetes insipidus above).

Pineal Gland

The pineal gland is a neuroendocrine structure situated midline in the subarachnoid space below the third ventricle with no blood–brain barrier (BBB). Its physiologic function is the secretion of melatonin, which is synthesized from serotonin. Melatonin is involved in the neurohumoral modulation of human sleep/wake cycles as well as pubescence. Currently, melatonin neurochemistry is an area of research interest. Adrenoglomerulotropin produced by the pineal gland is one of the triggers of aldosterone secretion. Tumors of the pineal gland may present for resection. Symptoms may include abnormal pubescence, gaze palsy, and increased ICP (due to obstructive of the cerebral aqueduct by the tumor). Respective operations may require the sitting position during surgery.

Insulin

Insulin is a peptide hormone secreted by the β-cells of the pancreas. It modulates glucose metabolism via a variety of receptors and signaling pathways. In certain disease states (e.g. metabolic syndrome (DM), infection, critical illness, and shock), the physiologic effects of insulin are decreased. Insulin exerts anti-inflammatory properties that may improve perioperative neurologic outcome. Glucose management using insulin for neurosurgical patients remains a controversial topic of high clinical interest. Optimal target ranges for glucose in the neurosurgical patient have not been determined. There is general agreement that severe hyperglycemia is both a marker
of injury severity and clinically deleterious in most settings. This is counter-balanced by concern of neurologic injury from hypoglycemia that frequently accompanies tight control regimens. In most cases a plasma glucose level greater than 150 mg/dL should be treated.

**Key Points**

**Additional Neuroendocrine Systems**

- Pheochromocytoma is a metabolically active neuroendocrine tumor associated with episodic severe hypertension
  - Suspect based on associated syndrome (neurofibromatosis I, MEN II, Von Hippel-Lindau) or symptoms
  - Diagnosis: plasma-free and urine metanephrines
  - Optimal perioperative management requires preoperative therapy with anti-catecholaminergic agents
- Acromegaly results from growth hormone excess
  - Tissue changes associated with growth hormone excess predispose patients to difficult airway management, and cardiomyopathy
- Insulin is a primary regulatory hormone of glucose metabolism
  - Insulin action is frequently impaired during physiologic stress or injury resulting in hyperglycemia
  - Hyperglycemia (>200 mg/dL) is deleterious in patients with neurologic injury
  - Treatment of hyperglycemia should target a moderate reduction to avoid the significant risks of plasma or cerebral hypoglycemia

**Suggested Reading**

Essentials of Neurosurgical Anesthesia & Critical Care
Strategies for Prevention, Early Detection, and
Successful Management of Perioperative Complications
Brambrink, A.M.; Kirsch, J.R. (Eds.)
2012, 200 p. 60 illus., 15 illus. in color., Softcover