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Endocrine Emergencies With Neurologic Manifestations

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ABSTRACT

Purpose of Review: This article provides an overview of endocrine emergencies with potentially devastating neurologic manifestations that may be fatal if left untreated. Pituitary apoplexy, adrenal crisis, myxedema coma, thyroid storm, acute hypercalcemia and hypocalcemia, hyperglycemic emergencies (diabetic ketoacidosis and hyperglycemic hyperosmolar state), and acute hypoglycemia are discussed, with an emphasis on identifying the signs and symptoms as well as diagnosing and managing these clinical entities.

Recent Findings: To identify the optimal management of endocrine emergencies, using formal clinical diagnostic criteria and grading scales such as those recently proposed for pituitary apoplexy will be beneficial in future prospective studies. A 2015 prospective study in patients with adrenal insufficiency found a significant number of adrenal crisis–related deaths despite all study patients receiving standard care and being educated on crisis prevention strategies, highlighting that current prevention strategies and medical management remain suboptimal.

Summary: Early diagnosis and prompt treatment of endocrine emergencies are essential but remain challenging because of a lack of objective diagnostic tools. The optimal management is also unclear as prospective and randomized studies are lacking. Additional research is needed for these clinical syndromes that can be fatal despite intensive medical intervention.

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INTRODUCTION

Endocrine emergencies are a collection of rare and extreme manifestations of common endocrine disorders that are often triggered by an inciting event, such as an acute infection. An endocrine emergency may be the first presentation of the underlying endocrine disorder. The neurologic and systemic complications of endocrine disorders generally worsen with increasing severity of the endocrine dysfunction. However, the rate of change is important, as rapid alterations may result in significant neurologic dysfunction, while severe but

chronic endocrine dysfunction may have only minimal symptoms. As many of these endocrine emergencies can be successfully managed if accurately and promptly diagnosed, clinical neurologists should be aware of the neurologic manifestations of endocrine disorders.

PITUITARY APOPLEXY

Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland and is most commonly associated with a pituitary adenoma.¹ Rarely, pituitary apoplexy can occur in

a normal pituitary gland, such as after a massive postpartum uterine hemorrhage leading to significant hypotension and infarction of the pituitary gland (Sheehan syndrome).² While incidentally found subclinical apoplexy is more frequent than acute apoplexy, with up to 25% of all pituitary tumors displaying hemorrhagic or necrotic areas on imaging or autopsy,¹ the focus here is on acute symptomatic pituitary apoplexy.

Epidemiology and Pathophysiology

Pituitary apoplexy occurs infrequently, with community-based studies finding a prevalence of 6.2 cases per 100,000 individuals and an incidence of 0.17 episodes per 100,000 per year.^{3,4} Approximately 2% to 12% of patients with all types of pituitary adenomas experience apoplexy, with the diagnosis of pituitary adenoma not previously known in more than 3 out of 4 cases.¹ Pituitary apoplexy is observed in all types of pituitary adenomas and particularly in macroadenomas, with the estimated risk of apoplexy in a conservatively managed nonfunctioning pituitary adenoma between 0.2 and 0.6 events per 100 person-years.^{5,6}

Precipitating factors associated with pituitary apoplexy have been identified in up to 40% of all reported cases and include angiographic procedures, surgical procedures, head trauma, pregnancy, and anticoagulant therapy.^{1,7} While anticoagulant therapy may incite pituitary apoplexy, a lack of well-designed prospective studies makes it difficult to give recommendations regarding anticoagulant therapy in patients with known pituitary adenomas.¹ Stimulation of the pituitary gland through dynamic testing (eg, insulin, gonadotropin-releasing hormone, growth hormone–releasing hormone, thyrotropin-releasing hor-

mone, and corticotrophin-releasing hormone) and certain hormonal treatments has been implicated in precipitating pituitary apoplexy (Case 8-1); however, whether dopamine agonists, which are commonly used in treating prolactinomas, can precipitate pituitary apoplexy remains controversial.^{1,8–10}

Clinical Presentation

Depending on the extent of hemorrhage, necrosis, and edema, the course of pituitary apoplexy can include very mild symptoms of headache, visual disturbances, or pituitary deficiencies developing slowly over weeks, or a true medical emergency presenting with acute onset of blindness, coma, and hemodynamic instability that can result in death if untreated.^{1,7} Headache is the most prominent and common symptom, occurring in more than 80% of patients, and is classically described as a thunderclap headache that is usually retroorbital but can be bifrontal or diffuse.¹ Visual disturbances are also common and affect more than half of all patients. Mass effect or abrupt pressure increase in the pituitary region caused by the apoplexy can cause visual deficits by superior extension with compression of the optic chiasm/optic nerves or lateral extension into the cavernous sinuses causing ocular motor palsies affecting cranial nerves III, IV, or VI.¹ Meningeal irritation can occur from the extravasation of blood or necrotic tissue into the subarachnoid space, leading to photophobia, nausea, vomiting, meningismus, and, sometimes, fever, as well as variable degrees of altered consciousness.¹ Cerebral ischemia is a rare complication that can be due to cerebral vasospasm or compression of the cerebral arteries, leading to focal neurologic deficits.¹¹ Endocrine dysfunction is common and can be present before the apoplexy. Corticotrophic deficiency occurs in 50%

KEY POINTS

- As endocrine emergencies can be successfully managed if accurately and promptly diagnosed, clinical neurologists should be aware of the neurologic manifestations of endocrine emergencies.
- Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland and is most commonly associated with a pituitary adenoma.
- Depending on the extent of hemorrhage, necrosis, and edema, the course of pituitary apoplexy can include very mild symptoms of headache, visual disturbances, or pituitary deficiencies developing slowly over weeks to a true medical emergency presenting with acute onset of blindness, coma, and hemodynamic instability that can result in death if untreated.

KEY POINT

- Lumbar puncture has limited utility in differentiating pituitary apoplexy from subarachnoid hemorrhage; however, if bacterial meningitis is suspected, CSF cultures should be obtained.

Case 8-1

A 65-year-old man with hypertension and prostate cancer presented to the hospital reporting headache and blurry vision. Three days earlier, he had received his first dose of depot leuprolide for androgen deprivation therapy. A few hours after the initial injection, he started to develop a mild headache and blurred vision. Both the headache and blurred vision worsened over the following days, prompting the patient to seek medical attention. He stated that his headache had now become persistent and unbearable, and he was now unable to move his right eye or raise his right eyelid.

Neurologic examination was notable for a right third cranial nerve palsy. MRI of the brain revealed a large intrasellar mass with hemorrhage. Blood was drawn for endocrine evaluation. Hydrocortisone was empirically administered, and the patient underwent transsphenoidal surgery for diagnosis and resection of the intrasellar mass. Pathology revealed that the tissue was necrotic and hemorrhagic, but viable tissue was positive for follicle-stimulating hormone, consistent with a gonadotroph pituitary adenoma. The patient was in stable condition after surgery and referred to endocrinology for additional evaluation and management.

Comment. This patient presented with new onset of worsening headache and blurry vision, with examination revealing a right oculomotor nerve palsy. While the differential diagnosis can be relatively broad, the use of leuprolide, a gonadotrophin-releasing hormone agonist, immediately before symptoms began suggests an association with the symptoms. In this case, the patient had a previously undiagnosed gonadotroph pituitary adenoma that, when stimulated by leuprolide, led to hemorrhage of the adenoma and the presenting symptoms. Because of the intense headaches and severe neuro-ophthalmologic symptoms, the patient was taken for urgent imaging and neurosurgical decompression. If the symptoms were mild and the patient was stable, a conservative medical approach may have been considered, as pituitary apoplexies can spontaneously resolve; however, the optimal management remains unclear without prospective studies comparing surgical to medical management.

to 80% of cases, with secondary adrenal insufficiency leading to potentially devastating hypotension and hyponatremia.¹ Other pituitary defects (eg, thyrotropic deficiency) are also commonly seen in patients with pituitary apoplexy, but they can usually be addressed after the acute neurologic and corticotropic deficiencies are resolved.^{1,7} Diabetes insipidus is rare and may be masked by secondary adrenal insufficiency or hypothyroidism.¹

Diagnosis and Management

The diagnosis of pituitary apoplexy relies on a combination of clinical assessment, endocrine testing, and radiologic

identification. The major differential diagnoses are subarachnoid hemorrhage and bacterial meningitis.¹ Lumbar puncture has limited utility in differentiating pituitary apoplexy from subarachnoid hemorrhage, as meningeal irritation caused by rupture of necrotic or hemorrhagic tissue from the apoplexy can cause pleocytosis, increased red blood cell count, and xanthochromia in the CSF;^{12,13} however, if bacterial meningitis is suspected, CSF cultures should be obtained. Patients with suspected pituitary apoplexy should have pretreatment endocrine testing, but treatment should not be delayed while waiting for these test results.⁷

Neuroimaging reflects the underlying pathologic process and can show a simple infarction, hemorrhagic infarction, mixed hemorrhagic infarction and clot, or pure clot.¹ Because of its wide availability, CT is often the initial emergency examination for patients with sudden-onset headache. While CT is diagnostic in only 21% to 28% of pituitary apoplexy cases, an intrasellar mass can be visualized in up to 80% of pituitary apoplexy cases.⁷ As most cases of pituitary apoplexy have a hemorrhagic component, a patchy or confluent area of hyperdensity can be seen by CT; however, the hyperdensity is not specific for pituitary apoplexy and may be seen with aneurysms, meningiomas, Rathke cleft cysts, germinomas, and lymphomas.¹⁴ Furthermore, if a few days have passed since the initial event, detecting hemorrhagic components of the pituitary apoplexy with CT may be difficult due to a decrease in blood density.¹ Contrast-enhanced CT can show a ring or inhomogeneous enhancement of the pituitary tumor.¹

MRI is the superior imaging modality for pituitary apoplexy as it can detect fresh blood accurately, correlates with histopathologic analysis, and confirms the diagnosis in over 90% of patients.^{7,15} Early changes seen on MRI include increased signal intensity on diffusion-weighted imaging in ischemic tissue.¹ Signal intensities on T1- and T2-weighted images depend on the presence (or absence) of hemorrhage and the stage (time after apoplexy) (Figure 8-1).¹⁴

Once a diagnosis is confirmed, acute pituitary apoplexy can be managed by either surgery or a more conservative medical approach. Surgical management consists of resecting the apoplectic pituitary mass with the goal of resolving the most emergent neurologic and visual symptoms. In the hands

of an experienced surgeon, overall complications are rare, but CSF leakage and (sometimes permanent) diabetes

KEY POINTS

- Empiric corticosteroid replacement should be initiated for patients with acute pituitary apoplexy with hemodynamic instability, altered consciousness, reduced visual acuity, severe visual field deficits, or signs of hypoadrenalism.
- Adrenal insufficiency can be classified as a primary disorder (eg, autoimmune destruction of the adrenal gland) or a secondary disorder (eg, hypopituitarism caused by pituitary apoplexy) or may result from drug-induced adrenal insufficiency (eg, glucocorticoid withdrawal after chronic exogenous glucocorticoid therapy).

insipidus may occur.¹ Because of reports of spontaneous clinical improvement and shrinkage of apoplectic pituitary adenomas, a conservative approach has been suggested in select cases with absent or mild and stable neuro-ophthalmic signs.^{1,7} Currently, no randomized prospective trials have been performed comparing the outcomes of surgery to conservative management to help guide treatment of patients with pituitary apoplexy; however, grading systems have recently been developed to better classify and improve the management of patients with pituitary apoplexy (**Figure 8-2** and **Table 8-1**).^{7,16} For all patients with pituitary apoplexy who have hemodynamic instability, altered consciousness, reduced visual acuity, severe visual field deficits, or signs of

hypoadrenalism, empiric corticosteroid replacement should be initiated and tapered to a maintenance dose once the patient recovers from the acute period.⁷ Additionally, patients will likely need long-term hormonal replacement because of the hypopituitarism caused by the apoplexy.¹⁷

ADRENAL CRISIS (ADDISONIAN CRISIS)

Adrenal insufficiency can be classified as a primary disorder (eg, autoimmune destruction of the adrenal gland) or a secondary disorder (eg, hypopituitarism caused by pituitary apoplexy) or may result more commonly from drug-induced adrenal insufficiency (eg, glucocorticoid withdrawal after chronic exogenous glucocorticoid therapy) (**Table 8-2**).¹⁸⁻²⁰ Primary adrenal

FIGURE 8-2

Flowchart illustrating assessment using the Pituitary Apoplexy Grading System.

GCS = Glasgow Coma Scale; p modifier = prolactinoma; r modifier = hemorrhagic Rathke cleft cyst; s modifier = significant comorbidities.

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TABLE 8-1 Pituitary Apoplexy Score^a

Variable	Points
Level of consciousness	
Glasgow Coma Scale 15	0
Glasgow Coma Scale 8–14	2
Glasgow Coma Scale <8	4
Visual acuity	
Normal (or no change from pre-pituitary apoplexy visual acuity)	0
Reduced, unilateral	1
Reduced, bilateral	2
Visual field deficits	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present unilateral	1
Present bilateral	2

^a Reprinted with permission from Rajasekaran S, et al, *Clin Endocrinol*.⁷ © 2010 Blackwell Publishing Ltd. onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2010.03913.x/full.

insufficiency is associated with both glucocorticoid and mineralocorticoid deficiency, whereas secondary adrenal insufficiency does not have mineralocorticoid deficiency as the renin-angiotensin-aldosterone system is intact.^{18,21} Adrenal insufficiency often presents with systemic symptoms and signs, such as fatigue, anorexia, weight loss, hyperpigmentation of the skin (in primary adrenal insufficiency), gastrointestinal symptoms, orthostatic hypotension, and electrolyte disturbances.¹⁸ Neurologic manifestations are generally nonspecific and neuropsychiatric

in nature (eg, depression or delirium), but patients may also present with muscle pain and weakness that may be secondary to electrolyte and metabolic problems.^{18,21} While adrenal insufficiency often manifests in an insidious nature, an acute adrenal crisis, or Addisonian crisis, is a true medical emergency and can lead to seizures, severe encephalopathy including coma, and death without prompt medical attention.

Epidemiology and Pathophysiology

Adrenal crisis occurs when, during an acutely stressful event, a patient with adrenal insufficiency fails to mount a normal physiologic response of increased endogenous cortisol production and is not adequately compensated with exogenous glucocorticoids.¹⁹ In a 2015 prospective study of patients with primary and secondary adrenal insufficiency receiving standard care, 8.3 adrenal crises per 100 patient-years and an alarmingly 0.5 adrenal crisis-related deaths per 100 patient-years were reported.²² A precipitating event triggering the adrenal crisis can be identified for the vast majority of patients (more than 90%), with gastrointestinal illness and fever from an acute infection being the most common.^{19,22} Other common precipitating events include surgical stress, emotional stress, and inadequate exogenous corticosteroid treatment, but, rarely, more benign-appearing events, such as flight delays and wasp bites, may trigger an adrenal crisis.¹⁹ The risk of adrenal crisis is likely to be higher in primary adrenal insufficiency compared to secondary adrenal insufficiency and may be the initial clinical presentation in up to 50% of patients with primary adrenal insufficiency.¹⁹ However, all patients with adrenal insufficiency, including drug-induced adrenal insufficiency, are at risk for adrenal crisis.¹⁹

KEY POINT

- Adrenal crisis occurs when, during an acutely stressful event, a patient with adrenal insufficiency fails to mount a normal physiologic response of increased endogenous cortisol production and is not adequately compensated with exogenous glucocorticoids.

TABLE 8-2 Etiology of Adrenal Insufficiency^a**► Primary Disorder: Addison Disease**

Autoimmune (sporadic, autoimmune polyendocrine syndrome type I and type II)
 Infections (eg, tuberculosis, fungal, human immunodeficiency virus [HIV])
 Metastatic tumors (eg, lung, breast, kidney, and, rarely, lymphoma)
 Congenital adrenal hyperplasia
 Adrenomyeloneuropathy/adrenoleukodystrophy
 Bilateral adrenal hemorrhage
 Bilateral adrenalectomy

► Secondary Disorder

Pituitary tumor or metastases to the pituitary gland
 Other tumors (eg, craniopharyngioma, meningioma) in the parasellar region
 Pituitary surgery or radiation
 Lymphocytic hypophysitis
 Head trauma
 Pituitary apoplexy/Sheehan syndrome
 Pituitary infiltration (eg, sarcoidosis, histiocytosis)
 Empty sella syndrome leading to pituitary dysfunction

► Glucocorticoid-induced Adrenal Insufficiency

Long-term exogenous glucocorticoid use

^a Modified with permission from Puar TH, et al, Am J Med.¹⁹ © 2016 Elsevier. sciencedirect.com/science/article/pii/S000293431500827X.

While chronic and higher doses of glucocorticoid have the highest risk for adrenal insufficiency after glucocorticoid withdrawal, a recent systemic review and meta-analysis found no administration form, dosing, treatment duration, or underlying disease for which adrenal insufficiency can be excluded.²³ Therefore, neurologists need to be vigilant when withdrawing glucocorticoids from their patients and test for adrenal insufficiency in any patients who develop unexplained symptoms after glucocorticoid withdrawal. Unfortunately, clinical evidence to support any specific glucocorticoid-tapering regimen to help avoid adrenal insufficiency is lacking. One reasonable option would be to stop without a taper after short-term (1 to 2 weeks) glucocorticoid use of any dosing in an otherwise

healthy and stable patient, followed by monitoring for any signs and symptoms of adrenal insufficiency. For patients with longer durations of glucocorticoid therapy, a slow steady taper over several weeks to months, depending on the duration and dose of glucocorticoid therapy, will likely be needed.

Clinical Presentation

In an adrenal crisis, patients often present with gastrointestinal symptoms, nausea, vomiting, muscle cramps, and hypotension, which may be erroneously diagnosed as gastroenteritis or an acute abdomen, potentially leading to a delay in treatment. Neurologic manifestations can include altered mental status (eg, delirium), convulsions, myopathy, and flexion contractures.²¹ Without prompt medical attention, patients can quickly

worsen to hypotensive shock and coma that can be fatal.^{19,20}

Typical laboratory findings include hyponatremia, hyperkalemia (in primary adrenal insufficiency), increased blood urea nitrogen (BUN) caused by prerenal failure, hypoglycemia (rare in adults and more common in children with primary adrenal insufficiency), and, rarely, hypercalcemia.^{19,20,24}

Diagnosis and Management

Treatment should be started immediately in patients with known adrenal insufficiency presenting with symptoms typical of an adrenal crisis.^{19,24} For medically unstable patients without a known diagnosis of adrenal insufficiency, treatment should not be delayed while waiting for a diagnosis, but, if possible, blood samples should be drawn just before the start of treatment for evaluation of serum levels of cortisol, adrenocorticotropic hormone (ACTH), aldosterone, dehydroepiandrosterone sulfate, and renin to help confirm the diagnosis.^{19,24} Testing for precipitating causes (eg, bacterial or viral infections) should also be initiated.²⁴

Fluid resuscitation and steroid replacement are the main therapies of an adrenal crisis.^{19,20,24} Prompt rehydration is needed to correct the hypovolemia and hyponatremia.^{19,20,24} Careful monitoring of sodium levels is needed to avoid rapid correction of hyponatremia and development of the osmotic demyelination syndrome.¹⁹ Steroid replacement should be urgently instituted.^{19,20,24} Once a patient is clinically stable, the glucocorticoid dose can be quickly tapered over 1 to 3 days to oral maintenance doses, and mineralocorticoid replacement should be restarted when the dose of hydrocortisone falls to less than 50 mg/d.^{20,24} Prompt recognition of an adrenal crisis and prevention of future adrenal crises

are critical in avoiding potentially fatal outcomes.^{19,24,25}

THYROID DISORDERS

Similar to the systemic manifestations, many of the neurologic complications resulting from thyroid disorders (eg, altered mental status in hypothyroidism) can be insidious in nature.¹⁸ However, both myxedema coma from severe untreated hypothyroidism and thyroid storm are acute medical emergencies requiring prompt identification of the thyroid disorder and any underlying inciting factor, as they are often fatal if left untreated.

Hypothyroidism and Myxedema Coma

Hypothyroidism is most commonly seen with autoimmune thyroiditis (Hashimoto disease) but can also be caused by severe dietary iodine deficiency or iatrogenic causes, including postablative thyroiditis in hyperthyroid patients, neck irradiation, and certain medications.¹⁸ The neurologic complications from hypothyroidism may present slowly and subtly at first, with cognitive impairment, neuromuscular deficits, or headache.¹⁸ However, an infection or another inciting factor in a hypothyroid patient can lead to an acute decompensation and a medical emergency known as myxedema coma, which commonly presents with hypothermia and significantly depressed mental status that can be fatal if left untreated.

Epidemiology and pathophysiology. Myxedema coma is a rare clinical entity, with an estimated incidence rate of 0.22 per million per year.²⁶ Perhaps because of its rarity, one study found that the diagnosis was missed in half of patients with myxedema coma during the initial emergency department stay.²⁷ Any delay in diagnosing myxedema coma can be fatal and may contribute to the high

KEY POINT

- Fluid resuscitation and steroid replacement are the main therapies of an adrenal crisis.

KEY POINTS

- Myxedema coma is typically triggered by a systemic illness, such as a pulmonary or urinary infection; congestive heart failure; stroke; trauma; or certain medications in a patient with previously undiagnosed or untreated hypothyroidism.
- The cardinal hallmarks of myxedema coma are hypothermia and depressed mental status or coma.

mortality rate of 20% to 30%.^{28,29} Typically, myxedema coma is triggered by a systemic illness, such as a pulmonary or urinary infection; congestive heart failure; stroke; trauma; or certain medications in a patient with previously undiagnosed or untreated hypothyroidism (Table 8-3).²⁸ Cold seems to be a strong inciting factor, as up to 90% of cases occur during the winter months.²⁹ Myxedema coma is more common in older women, with 80% occurring in women older than 60 years; however, rarely, younger patients, including pregnant women, may be affected.²⁸

TABLE 8-3 Factors Precipitating Myxedema Coma^a

- **Drugs**
 - Withdrawal of levothyroxine
 - Anesthetics
 - Sedative hypnotics
 - Narcotics
 - Amiodarone
 - Lithium carbonate
- **Infections, sepsis**
- **Stroke**
- **Congestive heart failure**
- **Low temperature**
- **Trauma**
- **Metabolic disturbances**
 - Acidosis
 - Hypoglycemia
 - Hyponatremia
 - Hypercapnia
- **Other**
 - Gastrointestinal bleeding
 - Excessive ingestion of raw bok choy

^a Modified with permission from Klubo-Gwiedzinska J, Wartofsky L, Med Clin North Am.²⁸ © 2012 Elsevier. sciencedirect.com/science/article/pii/S0025712512000168.

Clinical presentation. The cardinal hallmarks of myxedema coma are hypothermia and depressed mental status or coma (Case 8-2).²⁹ On presentation, patients can have extreme hypothermia (to 26.7°C [80°F]) that may mask an infection.²⁸ Physical examination often reveals extreme signs of hypothyroidism, including dry, brittle skin and hair; doughlike nonpitting edema; hoarse voice; macroglossia; and delayed reflexes. Hypotension and shock may be seen from decreased cardiac contraction and potentially fatal bradyarrhythmias.²⁹ Prolonged mechanical ventilation is usually needed for severe hypoventilation.²⁸ Gastrointestinal bleeding caused by myxedema-associated coagulopathy may also be seen.²⁹ Neurologic manifestations of myxedema coma include depressed mental status, cerebellar signs, and, in up to 25% of cases, seizures, including reports of status epilepticus.^{28,30} Patients may not initially present with frank coma but with milder signs of depressed mental status, only to gradually decline to a coma during the hospitalization. Laboratory testing often shows hyponatremia as well as anemia and acidosis.²⁸ Lumbar puncture often finds a high opening pressure with an elevated CSF protein level.²⁸ If an infection is suspected or if no obvious inciting factor that triggered the myxedema coma is found, cultures should be obtained to find a potential source of infection.

Diagnosis and management. Thyroid testing usually finds an abnormally high thyroid-stimulating hormone (TSH) level, but, as up to 10% of the hypothyroidism in myxedema coma can be due to hypothalamic or pituitary dysfunction, the TSH levels may be low or inappropriately normal.^{28,31} Free thyroid hormones (thyroxine [T₄] and triiodothyronine [T₃]) should therefore be measured in all patients with

Case 8-2

A 70-year-old woman with no known medical problems presented to the hospital with significantly depressed mental status. Five months earlier, she had told her daughter that she was starting to feel lethargic. A week before presentation, she mentioned feeling very cold and having difficulty staying warm during the winter weather. On the day of presentation, she was difficult to arouse and was immediately brought by ambulance to the hospital.

On examination, she was hypothermic to 35°C (95°F) and her blood pressure was 90/50 mm Hg with a heart rate of 90/min. She had dry, brittle skin and nonpitting edema in her face and hands. She was somnolent but arousable and diffusely areflexic. Laboratory evaluation revealed mild hyponatremia. Chest x-ray was negative, but urinalysis revealed leukocytes and gram-negative bacteria.

She was started on empiric antibiotics while waiting for urine cultures. Because of a high suspicion of myxedema coma, she was empirically started on IV thyroxine (T4) and stress dose hydrocortisone. The endocrine tests subsequently revealed primary hypothyroidism with a thyroid-stimulating hormone level greater than 100 mU/L (reference range 0.4 mU/L to 5.0 mU/L) and free T4 levels of 2 pmol/L (reference range 9 pmol/L to 23 pmol/L). The patient's condition gradually improved over the next several days. IV T4 therapy was transitioned to oral therapy, and the steroid was slowly tapered before the patient was discharged with close outpatient monitoring by an endocrinologist.

Comment. This patient presented with the cardinal hallmarks of myxedema coma, with hypothermia, depressed mental status, and signs and symptoms of hypothyroidism. The patient had no history of a thyroid disorder, but, as with this case, patients may be relatively asymptomatic or have undiagnosed hypothyroidism until an inciting factor, such as an infection, acutely precipitates the myxedema coma. Immediate recognition and treatment is critical, as myxedema coma has a high mortality rate.

KEY POINT

■ The main goal of treatment of myxedema coma should involve airway protection, thyroid hormone therapy, fluid repletion, empiric hydrocortisone because of the relative risk of adrenal insufficiency, correction of any hyponatremia, and treatment (including empiric antibiotics) of any inciting factors.

suspected myxedema coma to confirm hypothyroidism. Treatment should not be delayed while confirming the diagnosis. Because of the rarity of myxedema coma, no randomized clinical trials exist to guide its management; however, the main goal of treatment should involve airway protection, thyroid hormone therapy, fluid repletion, empiric hydrocortisone because of the relative risk of adrenal insufficiency, correction of hyponatremia, and treatment (including empiric antibiotics) of any inciting factors.²⁸ The optimal thyroid hormone therapy is controversial, with some advocating for the use of IV T4 (eg, 100 mcg to 500 mcg IV T4 followed by a maintenance dose of 50 mcg/d to 100 mcg/d until the patient

is able to tolerate an oral regimen) instead of T3 because of reports of increased mortality with T3.²⁹

Thyroid Storm (Thyroid Crisis)

Sustained thyrotoxicosis is most commonly due to Graves disease (auto-immune disease with antibody against TSH receptor) but may also be caused by a toxic multinodular goiter or TSH-secreting pituitary adenoma.¹⁸ The neurologic complications of thyrotoxicosis can vary and include neuropsychiatric impairment (eg, anxiety and restlessness), movement disorders (eg, tremor and, rarely, choreoathetosis),¹⁸ and neuromuscular disorders (eg, myopathy, periodic paralysis, and neuropathy) that often present

KEY POINTS

- Patients with thyroid storm have variable clinical manifestations, with exaggerated signs and symptoms of thyrotoxicosis accompanied by multiorgan decompensation.
- No set serum thyroxine (T4) or triiodothyronine (T3) criteria exist for diagnosing a thyroid storm, but a full laboratory evaluation including thyroid-stimulating hormone, free T3, and free T4 (even with a normal thyroid-stimulating hormone level) should be conducted in all suspected cases.

insidiously; however, a precipitating factor (eg, infection) can trigger a thyroid storm in a susceptible patient who is thyrotoxic, leading to a true medical emergency with exaggerated signs and symptoms of thyrotoxicosis, including severe encephalopathy.¹⁸

Epidemiology and pathophysiology.

The exact incidence of thyroid storm is difficult to accurately assess, but recent reports estimate that 1% to 2% of all hospital admissions for thyrotoxicosis are due to a thyroid storm.³² Thyroid storm most commonly affects women and those with Graves disease.³² The exact mechanisms leading to a thyroid storm are not known, but they likely involve an increased response to thyroid hormones, increased availability of free thyroid hormones, and enhanced binding of thyroid hormone to its receptor. Similar to myxedema coma, a precipitating factor, such as an infection or trauma, can trigger the thyroid storm in a patient who is thyrotoxic; however, 25% to 43% of patients presenting with a thyroid storm have no clear inciting factor.^{28,32} Factors precipitating thyrotoxic storm are listed in Table 8-4.

Clinical presentation. Patients with thyroid storm have variable clinical manifestations, with exaggerated signs and symptoms of thyrotoxicosis accompanied by multiorgan decompensation.³² Some of the cardinal manifestations include a high fever out of proportion to any infection; diaphoresis and tachycardia out of proportion to the fever; arrhythmias; and gastrointestinal symptoms, including nausea, vomiting, diarrhea, and possibly jaundice in severe cases.²⁸ Encephalopathy is commonly seen in the form of agitation, emotional lability, confusion, paranoia, psychosis, and eventually coma.²⁸ Additionally, cases of patients presenting with seizures or status epilepticus and stroke have been reported.³³ On laboratory evaluation, increased serum calcium

TABLE 8-4 Factors Precipitating Thyrotoxic Storm^a**► Drugs**

Withdrawal of antithyroid drug treatment
Radioactive iodine treatment
Thyroxine/triiodothyronine overdose
Cytotoxic chemotherapy
Aspirin overdose
Iodinated contrast dyes
Organophosphate toxicity

► Sepsis, infection**► Seizure disorder****► Pulmonary thrombo-embolism****► Burn injury****► Surgery, trauma, vigorous palpation of thyroid****► Metabolic disturbances**

Diabetic ketoacidosis
Hypoglycemia

► Other

Parturition
Emotional stress

^a Modified with permission from Klubo-Gwiedzinska J, Wartofsky L, Med Clin North Am.²⁸ © 2012 Elsevier. scienceirect.com/science/article/pii/S0025712512000168.

levels can be seen due to thyroid-mediated increased bone resorption.^{28,32} A moderate leukocytosis can be seen even in the absence of infection.

Diagnosis and management. The diagnosis of thyroid storm remains challenging and is largely based on clinical findings. No set serum T4 or T3 criteria exist for diagnosing a thyroid storm, but a full laboratory evaluation, including TSH, free T3, free T4, and electrolytes will be useful in establishing the thyrotoxicosis and associated electrolyte abnormalities.³² The goals of treatment of thyroid storm

are to inhibit new thyroid hormone synthesis (eg, with propylthiouracil or methimazole), inhibit thyroid hormone release (eg, with sodium iodine or lithium), block the peripheral effect of thyroid hormones (eg, with beta-blockers), and enhance the clearance of thyroid hormones (eg, with cholestyramine or plasma exchange).^{28,32} External cooling and acetaminophen may be needed for hyperthermia.³² Fluid resuscitation should be initiated for any volume depletion caused by fever, diarrhea, or vomiting.³² Stress dose steroids can be administered to prevent adrenal insufficiency as well as decrease the peripheral conversion of T4 to T3. Finally, an extensive and exhaustive investigation should be initiated to identify the inciting factor. As infection is a leading trigger of a thyroid storm, empiric antibiotic therapy may also be useful in the management of thyroid storm. Despite early diagnosis and intervention, thyroid storm has a high mortality rate, from 10% to 75% in patients who are hospitalized.²⁸

CALCIUM DISORDERS

Calcium homeostasis is normally tightly regulated by parathyroid hormone, calcitonin, and vitamin D.³⁴ The secretion of parathyroid hormone from the parathyroid gland is activated by low plasma calcium levels and inhibited by high plasma calcium levels. Parathyroid hormone increases calcium levels by activating osteoclasts, prompting the release of calcium from bone, increasing the activation of vitamin D, and stimulating reabsorption of calcium in the kidneys.³⁴ Vitamin D acts on the intestine to increase calcium absorption. In response to hypercalcemia, calcitonin is secreted by parafollicular C cells of the thyroid gland to inhibit osteoclast-mediated resorption of calcium in the bone.³⁴ Calcium disorders

can develop from any pathologic process that leads to dysfunction in intestinal calcium absorption, bone resorption, or renal calcium reabsorption or calcium excretion.

Hypercalcemia has long been associated with changes in mental status, with hypercalcemic crisis being a true medical emergency that can lead to coma and death.^{35,36} Similarly, acute hypocalcemia may present with neurologic manifestations, such as seizures requiring urgent evaluation and treatment.

Hypercalcemia

Hypercalcemia is a relatively common metabolic perturbation, affecting as many as 0.5% of all hospitalized patients, and is generally well tolerated if serum calcium levels are below 3.0 mmol/L (12 mg/dL).³⁷ However, higher or rapid elevation in serum calcium levels can lead to dysfunction in multiple organs, including the central nervous system.

Epidemiology and pathophysiology. The most common cause of hypercalcemia is underlying primary hyperparathyroidism caused by a single benign parathyroid adenoma, but hypercalcemia can result from malignancies, endocrinopathies, granulomatous diseases, immobilization, and medications such as thiazide diuretics and lithium (Table 8-5).³⁶ Hypercalcemic crisis typically results from an underlying mild to moderate hypercalcemia that evolves into an acute exacerbation of severe hypercalcemia, often triggered by an inciting factor such as an illness or thiazide diuretics.^{36,38} Overall, hypercalcemic crisis is a rare clinical entity, affecting a reported 1.6% to 6% of patients undergoing parathyroidectomy.³⁸

Clinical presentation. Hypercalcemia affects most organs, including the gastrointestinal system, resulting in anorexia, nausea, vomiting, dyspepsia,

KEY POINTS

- The goals of treatment of thyroid storm are to inhibit new thyroid hormone synthesis, inhibit thyroid hormone release, block the peripheral effect of thyroid hormones, and enhance the clearance of thyroid hormones.
- The most common cause of hypercalcemia is an underlying primary hyperparathyroidism caused by a single benign parathyroid adenoma, but hypercalcemia can result from malignancies, endocrinopathies, granulomatous diseases, immobilization, and medications such as thiazide diuretics and lithium.
- Hypercalcemic crisis usually results from an underlying mild to moderate hypercalcemia that evolves into an acute exacerbation of severe hypercalcemia, often with a known precipitating factor such as an illness or use of thiazide diuretics.

TABLE 8-5 Etiology of Hypercalcemia^a**► Parathyroid Disease**

Primary hyperparathyroidism due to benign parathyroid adenoma, parathyroid carcinoma, or parathyroid multiglandular hyperplasia as part of multiple endocrine neoplasia syndromes
Tertiary hyperparathyroidism

► Malignancy

Parathyroid hormone–related protein (humoral hypercalcemia of malignancy)
Local osteolysis mediated by cytokine release
Lytic bone metastasis
Multiple myeloma
Ectopic production of 1,25-dihydroxyvitamin D by the tumor (eg, lymphoma)

► Endocrinopathies

Adrenal insufficiency
Multiple endocrine neoplasia type 1, type 2A
Thyrotoxicosis
Pheochromocytoma
VIPoma (pancreatic endocrine tumor that secretes vasoactive intestinal peptide)

► Granulomatous Disease

Tuberculosis
Sarcoidosis
Endemic mycosis: histoplasmosis, coccidioidomycosis
Leprosy
Crohn disease
Berylliosis

► Medications

Estrogens
Lithium
Thiazide diuretics
Excess vitamin D or vitamin A ingestion

► Miscellaneous

Familial hypocalciuric hypercalcemia
Immobilization

^a Modified with permission from Ahmad S, et al, Am J Med.³⁶ © 2015 Elsevier. sciencedirect.com/science/article/pii/S0002934314009152.

and abdominal pain; pancreatitis that may be severe and necrotizing; and renal dysfunction with dehydration, polydipsia, oliguria, and nephrocalcinosis.³⁶ Cardiovascular abnormalities are often present (eg, arrhythmias, heart block, and vascular calcification).³⁶ Neurologic man-

ifestations are mainly neuropsychiatric/cognitive and neuromuscular in nature. Neuropsychiatric dysfunction can range from personality changes, such as irritability and depression, to lack of concentration, memory impairment, and, if the hypercalcemia is severe

enough, lethargy and coma.^{34–36} Neuromuscular symptoms include generalized fatigue and muscle weakness affecting primarily the proximal muscles.³⁴ Other rare reported neurologic manifestations include parkinsonism and posterior reversible encephalopathy syndrome (PRES) as well as clinical symptoms and EEG findings similar to those seen with Creutzfeldt-Jakob disease.^{39–41}

Diagnosis and management. While no uniform standard definition for hypercalcemic crisis exists, one reasonable but arbitrary definition is an albumin-corrected serum calcium level greater than 14 mg/dL associated with multi-organ dysfunction.³⁶ As approximately 40% of total serum calcium is bound to protein, primarily albumin, ionized (free) calcium levels (greater than 5.6 mg/dL) may be a more reliable assessment of calcium status if protein levels fluctuate, such as with sepsis.³⁷ Parathyroid hormone levels should be measured to determine if primary hyperparathyroidism is the etiology. If the parathyroid hormone level is only mildly elevated or inappropriately normal, then additional underlying processes should be considered (Table 8-5). However, in patients with acute and unstable hypercalcemic crisis, the appropriate treatment should not be delayed while trying to diagnose the underlying cause of the hypercalcemic crisis.

The overall goals of therapy are to lower calcium levels, rehydrate, increase renal calcium excretion, and decrease osteoclast-mediated bone resorption, followed by definitive curative therapy of the hypercalcemia (eg, parathyroidectomy in primary hyperparathyroidism).³⁶ Patients with hypercalcemic crises are hypovolemic.^{36,37} Adequate fluid resuscitation will lead to increased filtration of calcium and decreased reabsorption of calcium and promote calciuria in the kidneys. Fluid status

should be carefully monitored to avoid fluid overload and congestive heart failure, particularly in patients with cardiac or renal failure.³⁶ Historically, loop diuretics were administered to further promote calciuresis, but they are no longer recommended because of the risk of aggravating volume contraction, except in patients in whom the fluid resuscitation may have provoked cardiogenic fluid overload.^{36,42} Unless a contraindication exists, as soon as severe hypercalcemia is detected, all patients with hypercalcemic crisis should receive bisphosphonate therapy, which directly inhibits osteoclast activity but has a latency until reaching peak effect at 2 to 5 days.^{36,37} Calcitonin can be administered to rapidly lower calcium levels, particularly in patients who are acutely ill, but can cause a hypersensitivity reaction and tachyphylaxis, which can be minimized by coadministration of glucocorticoid therapy.³⁷ Glucocorticoid therapy may be useful in multiple myeloma and lymphoma-related hypercalcemia as well as in hypercalcemia resulting from elevated levels of 1,25-dihydroxyvitamin D as seen in granulomatous diseases.³⁶ Hypomagnesemia and hypophosphatemia may be present in primary hyperparathyroidism and should be corrected.³⁴ Once the patient is stable, definitive curative therapy, such as parathyroidectomy for primary hyperparathyroidism, should be expeditiously pursued.³⁶

Acute Hypocalcemia

Hypocalcemia can present with few, if any, symptoms, especially if the fall in calcium level is gradual. However, a significant reduction (to less than 7.5 mg/dL or 1.9 mmol/L) or a rapid rate of decline can lead to a true medical emergency with severe neurologic complications, including encephalopathy and seizures.

KEY POINT

■ The overall goals of therapy of a hypercalcemic crisis are to lower calcium levels, rehydrate, increase renal calcium excretion, and decrease osteoclast-mediated bone resorption, followed by definitive curative therapy of the hypercalcemia.

KEY POINT

■ Disorders of parathyroid hormone and vitamin D are the major causes of hypocalcemia, with acquired hypoparathyroidism as a complication of thyroid and neck surgeries being the most common cause of hypocalcemia in adults.

Epidemiology and pathophysiology. Disorders of parathyroid hormone and vitamin D are the major causes of hypocalcemia, with acquired hypoparathyroidism as a complication of thyroid and neck surgeries being the most common cause of hypocalcemia in adults (Table 8-6).^{34,43,44} The rate of hypoparathyroidism after total thyroidectomies is estimated to be from 0.5% to 6.6%.⁴³ Since calcium is bound to proteins, serum calcium levels can fall when serum protein is reduced, such as during volume overload, chronic illness, malnutrition, or nephrotic syndrome. Vitamin D is important for

intestinal calcium absorption, and severe vitamin D deficiency can also lead to significant hypocalcemia.^{34,44} Certain medications can also decrease calcium, such as antiepileptic drugs, chemotherapy drugs, and bisphosphonates.^{34,45} Hypomagnesemia can reduce parathyroid secretion or cause resistance to parathyroid hormone.³⁴

Clinical presentation. Systemic manifestations of hypocalcemia include myocardial dysfunction, such as prolongation of the QT interval on ECG and cardiomyopathy in long-standing hypocalcemia.^{46,47} Acute hypocalcemia can affect both the peripheral nervous

TABLE 8-6 Etiology of Hypocalcemia^a

► **Associated With Low Parathyroid Hormone**

Surgical hypoparathyroidism after thyroid, parathyroid, or radical neck surgery for head/neck cancer
Autoimmune hypoparathyroidism with or without polyendocrine syndrome type I
Parathyroid destruction from radiation or infiltrative diseases (eg, metastasis, sarcoidosis)
Postparathyroidectomy hungry bone syndrome
Familial syndromes (eg, DiGeorge syndrome, Kearns-Sayre syndrome, Kenny-Caffey syndrome)
Activating mutations of the calcium-sensing receptor gene
Hypomagnesemia
Severe hypermagnesemia

► **Associated With High Parathyroid Hormone**

Vitamin D deficiency or resistance
Renal disease
Drugs (eg, anticonvulsants, bisphosphonates)
Extravascular deposition (eg, acute pancreatitis)
Parathyroid resistance (eg, missense mutation in parathyroid hormone, pseudohypoparathyroidism, hypomagnesemia)
Osteoblastic metastases of breast and prostate cancer

► **Pseudohypocalcemia**

Hypoalbuminemia
Acid-base disturbances
Gadolinium-based contrast agents

^a Modified with permission from Agrawal L, et al, *Handb Clin Neurol*.³⁴ © 2014 Elsevier. science/article/pii/B9780702040870000498.

system and the central nervous system. Patients may present with finger paresthesia, perioral numbness, painful finger contractions that may mimic dystonia (carpopedal spasm), or even laryngospasm that can cause respiratory compromise.³⁴

Typical central nervous system manifestations of hypocalcemia are encephalopathy and seizures, both of which can be the initial manifestation of the hypocalcemia.^{34,45} In two reported cases, seizures were the first presenting symptom of hypocalcemia, appearing months to years after the thyroidectomy that had resulted in iatrogenic parathyroidectomy.⁴⁸ In a 2014 study of 70 patients with idiopathic hypoparathyroidism, seizures were common and present in 64.3% of patients, with the majority (86.7%) being generalized tonic-clonic seizures.⁴⁹ Seizures due to hypocalcemia can also occur in severe vitamin D deficiency, particularly in children and infants in developing countries due to dietary insufficiencies, while infants in developed countries presenting with hypocalcemic seizures are likely a result of an underlying endocrinologic etiology.⁴⁵ On examination, tetany or neuromuscular irritability caused by hypocalcemia can be demonstrated by eliciting the Chvostek sign (ipsilateral facial contraction after facial nerve percussion) or Trousseau sign (painful carpopedal spasm after inflating a sphygmomanometer placed on the upper arm above the systolic blood pressure for 3 minutes).⁴³ Increased intracranial pressure and papilledema may be present with hypocalcemia.⁵⁰

Diagnosis and management. Serum calcium levels are usually lower than 7.0 mg/dL (or ionized calcium level lower than 0.8 mmol/L) in patients with acute symptomatic hypocalcemia.⁴⁴ Hypoparathyroidism can be diagnosed in patients who are hypocalcemic when the parathyroid level is normal or inap-

propriately low once hypomagnesemia has been ruled out.⁴³ If the parathyroid hormone level is high, then other causes must be evaluated, including measuring vitamin D levels (Table 8-6).

Treatment for patients with acutely symptomatic hypocalcemia consists of IV calcium given as a bolus, followed by a slow continuous infusion, with the goal of maintaining serum calcium levels in the low-normal range.⁴³ Calcium gluconate is preferred over calcium chloride, because it causes less tissue necrosis if extravasated. Vitamin D supplementation is required for patients who are hypocalcemic with significant vitamin D deficiency or hypoparathyroidism. If hypomagnesemia is found, magnesium must be supplemented as hypomagnesemia can lead to parathyroid hormone resistance.³⁴

ACUTE GLYCEMIC DISORDERS

With the prevalence of diabetes mellitus increasing worldwide, complications resulting from diabetes mellitus are also increasing, including hyperglycemic crises and acute hypoglycemic episodes. As the brain relies almost entirely on glucose for its energy source, acute alterations in brain glucose levels can have a wide range of potentially devastating neurologic consequences, from profoundly depressed mental status to focal neurologic deficits that are often, but not always, reversible.^{51,52} Recognizing these crises is important, as patients may not know they are diabetic and any significant delay in treatment could be fatal.

Hyperglycemic Crises (Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State)

Hyperglycemic crises can be classified as either diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state, which are distinct clinical entities that require different clinical management.⁵³

KEY POINTS

- Typical central nervous system manifestations of hypocalcemia are encephalopathy and seizures, both of which can be the initial manifestation of the hypocalcemia.
- On examination, tetany or neuromuscular irritability caused by hypocalcemia can be demonstrated by eliciting the Chvostek sign (ipsilateral facial contraction after facial nerve percussion) or Trousseau sign (painful carpopedal spasm after inflating a sphygmomanometer placed on the upper arm above the systolic blood pressure for 3 minutes).
- Treatment for patients with acutely symptomatic hypocalcemia consists of IV calcium given as a bolus, followed by a slow continuous infusion, with the goal of maintaining serum calcium levels in the low-normal range.
- As the brain relies almost entirely on glucose for its energy source, insufficient glucose in the brain can have a wide range of potentially devastating neurologic consequences, from altered mental status to focal neurologic deficits that are often, but not always, reversible.

KEY POINTS

- Diabetic ketoacidosis is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.
- Hyperglycemic hyperosmolar state is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.
- The most common precipitant of diabetic ketoacidosis and hyperglycemic hyperosmolar state is infection, but other causes include omission of or inadequate insulin dosing, pancreatitis, myocardial infarction, stroke, and certain drugs (eg, corticosteroids, thiazide diuretics, sympathomimetics, and antipsychotics).
- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state classically present with polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and altered mental status.

Epidemiology and pathophysiology.

DKA is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.⁵⁴ The estimated annual incidence in the United States varies with age from 4 to 8 per 1000 patients in all age groups to 13.4 per 1000 patients in those younger than 30 years.⁵⁵ Hospital admission for DKA has increased by approximately 75% over the past 2 decades.⁵⁶ While DKA used to be seen almost exclusively in type 1 diabetes mellitus, it is now becoming more common in type 2 diabetes mellitus, with one-third of all DKA hospitalizations in the United States occurring in patients with type 2 diabetes mellitus.⁵⁵ The overall mortality rate of DKA in adults in the United States is less than 1% and slightly higher than 5% in the elderly and patients with severe comorbid medical conditions; however, DKA remains a significant cause of mortality in children and young adults with type 1 diabetes mellitus.⁵⁵

Hyperglycemic hyperosmolar state is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.⁵⁴ Hyperglycemic hyperosmolar state is most commonly seen in older patients with type 2 diabetes mellitus but can be seen in younger patients and in patients with type 1 diabetes mellitus.^{53,55} The mortality rate in hyperglycemic hyperosmolar state is generally higher than in DKA, with estimates ranging between 5% and 20% in the United States and United Kingdom.^{53,54}

In DKA, the absolute or relative insulin deficiency combined with an increase in counterregulatory hormones (eg, glucagon, growth hormone, cortisol, and catecholamines) results in hyperglycemia, ketonemia, and metabolic acidosis.⁵⁶ The pathogenesis of hyperglycemic hyperosmolar state is less

well understood, but a greater degree of dehydration appears to exist due to osmotic diuresis. Importantly, in hyperglycemic hyperosmolar state, despite a relative insulin deficiency resulting in inadequate glucose utilization, endogenous insulin secretion appears to be greater than in DKA and is adequate to prevent lipolysis and subsequent ketogenesis.⁵⁴ Despite the different etiologies, both DKA and hyperglycemic hyperosmolar state frequently have an inciting factor that triggers the crisis. The most common precipitant of DKA and hyperglycemic hyperosmolar state is infection, but other causes include omission of or inadequate insulin dosing, pancreatitis, myocardial infarction, stroke, and certain drugs (eg, corticosteroids, thiazide diuretics, sympathomimetics, and antipsychotics).^{54,55} In the elderly, immobilization or an illness that restricts water intake can contribute to severe dehydration and hyperglycemic hyperosmolar state.⁵⁵ In young patients with type 1 diabetes mellitus, psychological and eating disorders are contributing factors in 20% of recurrent DKA.⁵⁴ Both DKA and hyperglycemic hyperosmolar state are associated with an inflammatory state with elevation of proinflammatory cytokines, which may explain the relatively high incidence of thrombotic events during a hyperglycemic crisis.⁵⁵

Clinical presentation. A major difference in clinical presentation between DKA and hyperglycemic hyperosmolar state is that the metabolic alterations in DKA usually evolve in less than 24 hours, while a hyperglycemic hyperosmolar state typically evolves over several days to weeks.⁵⁴ In both conditions, the hyperglycemic crisis can be the presenting manifestation of the underlying diabetes mellitus. Both DKA and hyperglycemic hyperosmolar state classically present with polyuria, polydipsia, weight loss,

vomiting, dehydration, weakness, and altered mental status.^{54,56} Gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, are frequent in DKA but uncommon in hyperglycemic hyperosmolar state.⁵⁴

On examination, patients may have poor skin turgor, tachycardia, hypotension, and Kussmaul respirations (deep and labored breathing associated with metabolic acidosis in DKA).^{54,56} Altered mental status can be severe, including significant lethargy and coma, which are more common in a hyperglycemic hyperosmolar state and correlate with hyperosmolality.⁵⁴ Seizures, including *epilepsia partialis continua*, and focal neurologic signs such as hemichorea and hemiballismus have also been reported in patients with a hyperglycemic hyperosmolar state (Figure 8-3).^{57,58} Even if an infection was the inciting cause for the hyperglycemic crisis, patients can be normothermic or

even hypothermic due to peripheral vasodilation.⁵⁴

Diagnosis and management. The diagnosis of DKA and hyperglycemic hyperosmolar state can be made with the appropriate clinical picture and biochemical tests (Table 8-7 and Table 8-8).^{53,55} Patients may have a mildly elevated leukocytosis due to proinflammatory changes associated with DKA and hyperglycemic hyperosmolar state; however, if the leukocytosis is greater than 25,000/mm³, then investigations into finding the source of an infection should be initiated.⁵⁶ Finding and treating any underlying infection is critical as mortality in DKA and hyperglycemic hyperosmolar state is rarely due to metabolic complications but from the underlying inciting illness.⁵⁴ Nonspecific elevations in serum amylase and lipase levels can be seen in approximately 15% to 25% of patients with DKA.⁵⁹

KEY POINT

■ Both diabetic ketoacidosis and hyperglycemic hyperosmolar state can be associated with altered mental status, including lethargy and coma. These are more common in hyperglycemic hyperosmolar state and correlate with hyperosmolality.

FIGURE 8-3

Brain CT (A) and brain MRI (B) of a patient with hemichorea-hemiballismus secondary to a hyperglycemic-hyperosmolar state. CT shows hyperdensity in the left caudate and putamen, which was confirmed by subsequent T1-weighted MRI.

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TABLE 8-7 Diagnostic Criteria for Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State^a

Diagnostic Criteria and Classification	Diabetic Ketoacidosis			Hyperglycemic Hyperosmolar State
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–15	<10	>15
Urine ketone	Positive	Positive	Positive	Small
Serum ketone	Positive	Positive	Positive	Small
Effective serum osmolality	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Variable

^a Modified with permission from Nyenwe EA, Kitabchi AE, Diabetes Res Clin Pract.⁵⁵ © 2011 Elsevier. sciencedirect.com/science/article/pii/S0168822711005146.

KEY POINT

- The goals of therapy in hyperglycemic crises are to correct the dehydration, hyperglycemia, and electrolyte abnormalities and to identify and treat the underlying inciting factor.

The goals of therapy in DKA and hyperglycemic hyperosmolar state are to correct the dehydration, hyperglycemia, and electrolyte abnormalities and to identify and treat the underlying inciting factor.^{53,54,56} Fluid resuscitation should begin with the goal of replacing approximately half of the water deficit in 12 hours.^{53,56} Close hemodynamic and laboratory moni-

toring are critical to ensure that rapid changes and overcorrection leading to hypoglycemia and hypokalemia are avoided. Hydration alone has been shown to be sufficient to reduce blood glucose and osmolality.⁵³ Adequate fluid replacement is essential before starting insulin, as a risk of potentially devastating cardiovascular collapse exists if insulin is administered before

TABLE 8-8 Water and Electrolyte Deficits in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State^a

Typical Deficits	Diabetic Ketoacidosis	Hyperglycemic Hyperosmolar State
Total water (L)	6	9
Water (mL/kg of body weight)	100	100–200
Serum sodium (mEq/L)	7–10	5–13
Cl [−] (mEq/L)	3–5	5–15
K ⁺ (mEq/L)	3–5	4–6
PO ₄ (mmol/L)	5–7	3–7
Mg ²⁺ (mEq/L)	1–2	1–2
Ca ²⁺ (mEq/L)	1–2	1–2

^a Modified with permission from Nyenwe EA, Kitabchi AE, Diabetes Res Clin Pract.⁵⁵ © 2011 Elsevier. sciencedirect.com/science/article/pii/S0168822711005146.

adequate volume resuscitation. IV insulin therapy should be initiated in all patients with DKA or hyperglycemic hyperosmolar state who are acutely ill and transitioned to subcutaneous insulin when the hyperglycemic crisis is resolved.^{53,56} Criteria for resolution of the ketoacidosis in DKA include a blood glucose less than 200 mg/dL and two of the following: a serum bicarbonate level of 15 mEq/L or higher, a venous pH higher than 7.3, and a calculated anion gap of 12 mEq/L or less.⁵⁴ A hyperglycemic hyperosmolar state is considered resolved when serum osmolality is normal and mental status returns to baseline.⁵⁴ One notable neurologic complication of DKA is cerebral edema, occurring in 0.7% to 1.0% of all DKA episodes in children, especially in those with newly diagnosed diabetes mellitus but also rarely in young adults under 20 years of age.⁵⁶ Headache is one of the earliest symptoms of cerebral edema, followed by rapid deterioration including lethargy, seizures, pupillary changes, papilledema, bradycardia, elevation in blood pressure, and respiratory distress.^{54,56} Mortality is extremely high once neurologic symptoms manifest. To prevent cerebral edema, excess hydration and rapid reduction of plasma osmolality and blood glucose levels should be avoided.⁵⁴

Hypoglycemia

Hypoglycemia is probably the most common endocrine emergency and is associated with significant autonomic and neurologic complications in the acute setting, which, if left untreated, could have devastating consequences.^{60, 61}

Epidemiology and pathophysiology. The most common cause of hypoglycemia is the inadvertent or deliberate overdose of hypoglycemic agents; less commonly, insulin-secreting tumors, Addison disease, renal or hepatic failure, or severe sepsis can cause symp-

tomatic hypoglycemia.^{51,60} Significant hypoglycemia is common in type 1 diabetes mellitus, with a prevalence of 36% reported in one prospective study of 411 patients.⁶² Patients with insulin-treated type 2 diabetes mellitus are also at risk for significant hypoglycemia, with one large study by the UK Hypoglycaemia Study Group finding an annual prevalence of 7%.⁶³

Clinical presentation. Acute significant hypoglycemia can have widely varying presentations, with the most common being autonomic and neurologic symptoms. Patients having an acute hypoglycemic episode tend to initially have autonomic symptoms of sweating, anxiety, nausea, and palpitations followed by the neurologic symptoms.⁶⁴ Initial neurologic symptoms can include drowsiness, fatigue, visual changes, and cognitive changes (eg, erratic and irrational behavior), which, if left untreated, can lead to seizures and coma.^{51,64} Rarely, the hypoglycemia can result in focal neurologic deficits that mimic stroke both clinically and on brain MRI.^{60,65}

Diagnosis and management. Hypoglycemia may lead to acute neurologic symptoms, particularly when the blood glucose level is below 70 mg/dL (3.9 mmol/L).⁶⁶ In symptomatic patients who are awake, oral fast-acting carbohydrates should be the initial treatment. Patients who are comatose should first receive empiric IV thiamine for possible Wernicke-Korsakoff syndrome, followed by IV dextrose-containing solutions, with close monitoring to avoid rebound hyperglycemia.⁶¹ If venous access is not available, subcutaneous or IM glucagon can be given.⁶¹ While the majority of hypoglycemia is from adverse effects of antidiabetic medications, other rare causes (eg, an insulin-secreting tumor) should be investigated as needed. Prevention of any future hypoglycemia in patients with diabetes mellitus requires

KEY POINT

■ The most common cause of hypoglycemia is the inadvertent or deliberate overdose of hypoglycemic agents, but, less commonly, insulin-secreting tumors, Addison disease, renal or hepatic failure, or severe sepsis can cause symptomatic hypoglycemia.

a combination of patient education, dietary intervention, exercise management, medication adjustment, glucose monitoring, and clinical surveillance by the medical provider.⁶⁶

CONCLUSION

Endocrine emergencies can present with acute and devastating neurologic manifestations such as seizures and coma, which, if left untreated, are often fatal. Many patients with endocrine emergencies have an undiagnosed underlying endocrine disorder that is acutely worsened by an inciting factor, such as a systemic infection. Therefore, accurately and promptly diagnosing and treating the endocrine disorder and any underlying inciting factor are paramount. As these endocrine emergencies are only infrequently encountered and many do not have a specific objective diagnostic test, a high degree of suspicion is needed to avoid missing the diagnosis. Furthermore, because of the overall rarity of endocrine emergencies, prospective or randomized clinical studies are lacking. Therefore, optimal management is sometimes unclear or controversial. Future studies of endocrine emergencies are clearly needed to help optimize both the diagnosis and the treatment of these disorders.

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