Chapter 23

Neurologic complications of electrolyte disturbances and acid–base balance

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INTRODUCTION

The complex interplay between respiratory and renal function is at the center of the electrolytic and acid-based environment in which the central and peripheral nervous systems function. Neurological manifestations are accompaniments of all electrolytic and acid–base disturbances once certain thresholds are reached (Riggs, 2002). This chapter reviews the major changes resulting from alterations in the plasma concentration of sodium, potassium, calcium, magnesium, and phosphorus as well as from acidemia and alkalemia (Table 23.1).

HYPONATREMIA

History and terminology

Hyponatremia applies to a plasma sodium concentration of less than 135 mmol/L. As sodium is the major osmotically active solute in the extracellular compartment, hyponatremia is of concern to neurologists insofar as it may reduce plasma osmolality below 285 mmol/L. In the setting of hypo-osmolality, water osmotically flows from the plasma and interstitial fluid into the intracellular compartment, with resulting intracellular edema and decreased cellular function (Adrogue and Madias, 2000b). Hence, the main concern with hyponatremia is the potential induction of *brain edema and secondary intracranial hypertension* (Nathan, 2007). Sodium and osmolality should *both* be low in the presence of true hyponatremia (hypotonic). *Pseudohyponatremia* occurs in the setting of hyperlipidemia or hyperproteinemia, when the plasma osmolality is normal (isotonic), or with hyperglycemia or mannitol intake, when plasma osmolality is high (hypertonic) due to the presence of either of these osmotically active substances (Weisberg, 1989; Lippi and Aloe, 2010). *True* or hypotonic hyponatremia is always due to a relative excess of water compared to sodium, and can occur in the setting of hypovolemia, euvolemia, and hypervolemia (Table 23.2), invariably reflecting an abnormal relationship between water and sodium, whereby the former is retained at a rate faster than the latter (Milionis et al., 2002). Homeostatic mechanisms protecting against changes in volume and sodium concentration include sympathetic activity, the renin–angiotensin–aldosterone system, which cause resorption of sodium by the kidneys, and the hypothalamic *arginine vasopressin*, also known as antidiuretic hormone (ADH), which prompts resorption of water (Eiskjaer et al., 1991). The release of ADH from its storage in the neurohypophysis is activated when the plasma volume is low and/or osmolality high, and acts by decreasing the maximum daily urine volume and correspondingly increasing the minimum urinary concentration (Kjaer, 1996). If ADH activity is very low, as much as 12 L of urine may be excreted daily and the minimum urinary concentration can be as little as 50 mmol/L. If ADH activity is at its maximum, only 0.5 L of urine can be excreted daily and the minimum urinary concentration may be as high as 1200 mmol/L (Robertson, 2006). Increased ADH activity, maximally limiting excretion of water, is the most common cause of hyponatremia. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is used to identify excessively released ADH despite normal plasma volume.

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Table 23.1

Major electrolyte and acid–base disturbances

	Definition	Major neurological manifestation	Perils of rapid or aggressive treatment
Hyponatremia	Sodium < 135 mmol/L Osmolality < 285 mmol/L	Muscle cramps, hyporeflexia, encephalopathy, seizures	Central pontine myelinolysis
Hypernatremia	Sodium > 145 mmol/L Osmolality > 295 mmol/L	Weakness, hyperreflexia, rigidity, tremor, chorea, or myoclonus and encephalopathy with seizures	Brain edema with seizures and coma
Hypokalemia	Potassium < 3.5 mmol/L	Weakness with normal reflexes, ascending weakness with sparing of cranial nerves, paresthesias	Cardiac arrhythmias; hypocalcemic tetany with concurrent hypocalcemia
Hyperkalemia	Potassium > 5 mmol/L	Weakness with hyporeflexia, ascending weakness with sparing of cranial nerves, burning paresthesias	Cardiac arrhythmias, especially when failing to coadminister calcium
Hypocalcemia	Calcium < 8.2 mg/dL Ionized calcium < 4.4 mg/dL	Tetany, trismus, opisthotonus, encephalopathy, seizures, Chvostek's sign, Trousseau's sign	Digitalis toxicity in patients on digoxin
Hypercalcemia	Calcium > 10.5 mg/dL	Encephalopathy, myoclonus, rigidity, proximal weakness and hyperreflexia	Furosemide may worsen hypercalcemia in the presence of heart failure
Hypomagnesemia	Magnesium < 0.6 mmol/L	Tetany with Chvostek's and Trousseau's signs, encephalopathy, seizures, hyperreflexia, tremor, chorea, and myoclonus with startle	Weakness
Hypermagnesemia	Magnesium > 2 mmol/L	Acute flaccid areflexic paralysis with respiratory insufficiency (may mimic a midbrain syndrome)	Ischemic heart disease, arrhythmias, pre-eclampsia, asthma
Hypophosphatemia	Phosphorus < 0.8 mmol/L	Acute areflexic paralysis with diaphragmatic, pharyngeal, facial, and extraocular weakness preceded by perioral paresthesias	Hypocalcemia-related complications
Acidosis	Serum pH < 7.35	Encephalopathy, visual impairment, asterixis, increased intracranial pressure (papilledema)	Hypokalemic arrhythmias if potassium is not replaced prior to insulin in diabetic ketoacidosis
Alkalosis	Serum pH > 7.44	Encephalopathy, seizures, tremor, myoclonus, circumoral/limb paresthesias, Chvostek's sign, tetany, hyperreflexia	Failure to correct hypocalcemia first may lead to hypocalcemic tetany

Acute areflexic flaccid paralysis with respiratory insufficiency can occur in hypermagnesemia and hypophosphatemia. Untreated hyperkalemia may cause chronic flaccid quadriplegia. Instead, hypokalemia, hypernatremia, and hypercalcemia lead to hypereflexic weakness. Derangements in potassium and hypermagnesemia do not affect the central nervous system. Sodium disorders, hypocalcemia and hypomagnesemia are common causes of encephalopathy *with* seizures. Hypercalcemia produces encephalopathy *rarely* with seizures (Castilla-Guerra et al., 2006).

Clinical findings

More than any other electrolytic disturbance, the symptoms and signs of hyponatremia are primarily neurologic due to the resulting cerebral edema (Table 23.3). In acute hyponatremia, occurring within 48 hours, the rapid brain adaptation (see section on pathophysiology) is insufficiently compensatory and patients are more likely to be symptomatic. Chronic, slow reductions in sodium concentration occurring over days to weeks allow the brain to adapt and patients to remain asymptomatic or have only subtle findings on neurological examination. Consequently, the sodium level is not a good predictor of whether a patient will be symptomatic: relatively mild hyponatremia (e.g., 125 mmol/L) can cause seizures and

Table 23.2

True (hypotonic) hyponatremia in the three volume states

	Hypovolemia	Normovolemia	Hypervolemia
Disorders	Renal: diuretic excess, renal tubular acidosis Extrarenal: diarrhea, vomiting, burns	Psychogenic polydipsia Hypothyroidism Adrenal insufficiency SIADH	Renal failure Nephrotic syndrome Congestive heart failure Liver failure Excessive water intake
Urine sodium* low: <20 mmol/L high: >20 mmol/L	Renal: high Extrarenal: low	Polydipsia: high Other disorders: low	Renal failure: high Other disorders: low
Treatment	Plasma volume restoration: isotonic saline (0.9% NaCl)	Chronic: fluid restriction to correct sodium at < 12 mmol/L per day Acute: IV furosemide, hypertonic saline (3% NaCl) to correct sodium at 1–2 mmol/L/hour	Correction of underlying disorder; fluid restriction

*Urine sodium concentration is a not a reliable marker of volume status in patients with renal failure, increased renal fluid loss from diuretics, or metabolic alkalosis.
SIADH, syndrome of inappropriate secretion of antidiuretic hormone, IV, intravenous.

Table 23.3

Symptoms and signs of hyponatremia

Symptoms	Signs
Nausea, vomiting	Seizures
Anorexia	Coma
Headaches	Hyporeflexia
Lethargy	Cheyne–Stokes respiration
Disorientation	Respiratory depression
Muscle cramps	Hypothermia

coma if it develops within 48 hours. Conversely, a patient with more severe hyponatremia (e.g., 118 mmol/L) may be asymptomatic if it has developed it over weeks or months.

In order of severity, patients may develop anorexia, nausea, and vomiting, followed by headache, blurred vision, lethargy and disorientation, irritability, and muscle cramps. Abnormal sensorium, seizures, and coma may ultimately develop (Lien and Shapiro, 2007). Left untreated, progressive cerebral edema may lead to brain herniation (Mulloy and Caruana, 1995). Hyporeflexia and muscle cramps are helpful clinical features that are more often present in hypo- than hypernatremia.

Laboratory investigations

Plasma osmolality may be normal, that is, between 285 and 295 mmol/L (hyperlipidemia or hyperproteinemia), or high, greater than 295 mmol/L (hyperglycemia or mannitol administration) in cases of pseudohyponatremia, where the treatment differs radically to what is laid out below. Plasma osmolality can be calculated using the formula:

$$2 \times [\text{sodium}]\,\text{mmol/L} + [\text{BUN}]\,\text{mg/dL}/2.8 + [\text{glucose}]\,\text{mg/dL}/18$$

Plasma osmolality less than 285 mmol/L confirms the presence of true (hypotonic) hyponatremia (Hoorn et al., 2005). Besides plasma osmolality, ascertaining volume status helps to narrow the differential diagnosis. In *hypovolemic hyponatremia*, urine sodium concentration can be used to distinguish renal from extrarenal fluid loss. Only in renal hypovolemia, such as in renal failure or in the setting of diuretic use, may patients have a urine sodium concentration >20 mmol/L (kidneys are unable to concentrate urine by retaining sodium) (Reddy and Mooradian, 2009). Extrarenal volume losses, when urine sodium concentration is <20 mmol/L, may be due to diarrhea, vomiting, pancreatitis, or burns. In *normovolemic hyponatremia*, the shortlist of diagnostic possibilities includes SIADH, hypothyroidism, adrenal insufficiency, or psychogenic polydipsia. Low urine sodium and low urine osmolality imply psychogenic polydipsia (Dundas et al., 2007). If urine sodium and osmolality are high, then a TSH and cosyntropin stimulation test will evaluate whether thyroid and adrenal function are depressed. A high TSH is diagnostic of hypothyroidism. The cosyntropin test consists of injecting a small amount of synthetic ACTH followed by measurement of cortisol. An inadequate cortisol response is diagnostic of adrenal insufficiency (Dorin et al., 2003). If the TSH and cosyntropin stimulation test results are normal, then SIADH must be

Table 23.4

Etiologies of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

CNS disorders	Extraneuronal	Iatrogenic
Autoimmune: Guillain–Barré syndrome, multiple sclerosis Infectious: brain abscesses, encephalitis, meningitis, HIV Vascular: stroke, subarachnoid hemorrhage, subdural hematoma	Ectopic production: duodenal cancer, pancreatic cancer, small cell lung cancer Pulmonary disease: acute asthma, pneumothorax, atelectasis, pneumonia, empyema, tuberculosis, *Pneumocystis carinii*, and *legionella*	Antipsychotics (haloperidol, thioridazine, chlorpromazine, trifluoperazine),* nonantipsychotic phenothiazines (promethazine, prochlorperazine), desmopressin, oxytocin, tricyclics (amitriptyline), SSRIs, opiates, carbamazepine, vincristine, cyclophosphamide, oral hypoglycemics (tolbutamide, chlorpropamide)

*Patients on antipsychotics may also be prone to developing two other causes of hyponatremia: psychogenic polydipsia and dry-mouth sensation due to their anticholinergic properties.

CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor; HIV, human immunodeficiency virus.

present. SIADH is confirmed in the setting of euvolemic, hypotonic hyponatremia, when the urine sodium is >20 mmol/L and the urine osmolality is >200 mmol/L higher than plasma (Fenske and Allolio, 2010) Confirming inappropriate release of ADH in the absence of hypovolemia or hyperosmolality (the usual stimuli for ADH release) requires investigations for a large number of etiologies, including autoimmune, infectious, vascular, and iatrogenic disorders (Table 23.4) (De and Demanet, 1976; Hannon and Thompson, 2010).

Pathophysiology

Hyponatremia causes osmotic shifts of water from the hypotonic extracellular compartment into the relatively hypertonic intracellular compartment, with resulting brain edema, decreased cerebral blood flow, and cerebral compression (Hoorn and Zietse, 2008). The increased pressure from brain edema causes fluid to move from the interstitium into the cerebral spinal fluid (CSF). The shunting of CSF to the systemic circulation relieves some of the intracranial pressure. Also, in hypovolemic hyponatremia, where symptoms are due to hypovolemia rather than hyponatremia, volume depletion stimulates ADH release, which limits the excretion of water (Hoorn and Zietse, 2008). Additional adaptive responses include releasing intracellular potassium (rapid adaptation) and organic solutes or *osmolytes* such as inositol, glutamine, glutamate, and taurine (slow adaptation, 24–48 hours after onset of hyponatremia), in an effort to decrease the osmotic gradient drawing water into the neurons (Diringer and Zazulia, 2006).

Management

Slow correction of hyponatremia (8–10 mmol/L/day) is always preferred with normal saline (0.9%). Too slow a correction, however, may lead to death from brain edema (Vaidya et al., 2010). Rapid correction of the hypotonic state may lead to brain shrinkage and osmotic demyelination of pontine and/or extrapontine neurons (*central pontine or extrapontine myelinolysis (CPM)*) that can express as quadriplegia, pseudobulbar palsy, seizures, coma, and death (Mount, 2009). The more severe and chronic the hyponatremia, and the faster the correction rate, the likelier it becomes that CPM may develop (Brunner et al., 1990). This complication of rapid correction of chronic hyponatremia is more common among those with comorbid alcoholism, malnutrition, hypokalemia, liver disease, and malignancy (Dellabarca et al., 2005; Heng et al., 2007). Similar complications may occur during rapid osmotic shifts in plasma (Fig. 23.1). In acute hyponatremia, when brain adaptation has not fully occurred, rapid correction is warranted and risk of central pontine or extrapontine myelinolysis is minimal (Soupart and Decaux, 1996).

Treatment is also guided by volume status since the focus of correction varies from restoration of normal plasma volume in hypovolemic hyponatremia to treating the underlying disorder in hypervolemic hyponatremia (Table 23.2). In normovolemic hyponatremia, the primary goal of correcting acute symptomatic (rapidly) and chronic asymptomatic hyponatremia (gradually, no faster than 0.5 mmol/L per hour or 12 mmol/L per 24 hours) is restricting water intake to below the maximum daily urine volume (Soupart and Decaux, 1996). The *water excess* to be removed by this *water restriction* strategy in both acute symptomatic and chronic asymptomatic hyponatremic patients can be calculated as follows:

$$\text{Weight (kg)} \times [0.6 \text{ in men OR } 0.5 \text{ in women}] \times (1 - [\text{sodium}]/125)$$

In addition to water restriction, strategies to *increase maximum daily urine* are employed in patients with
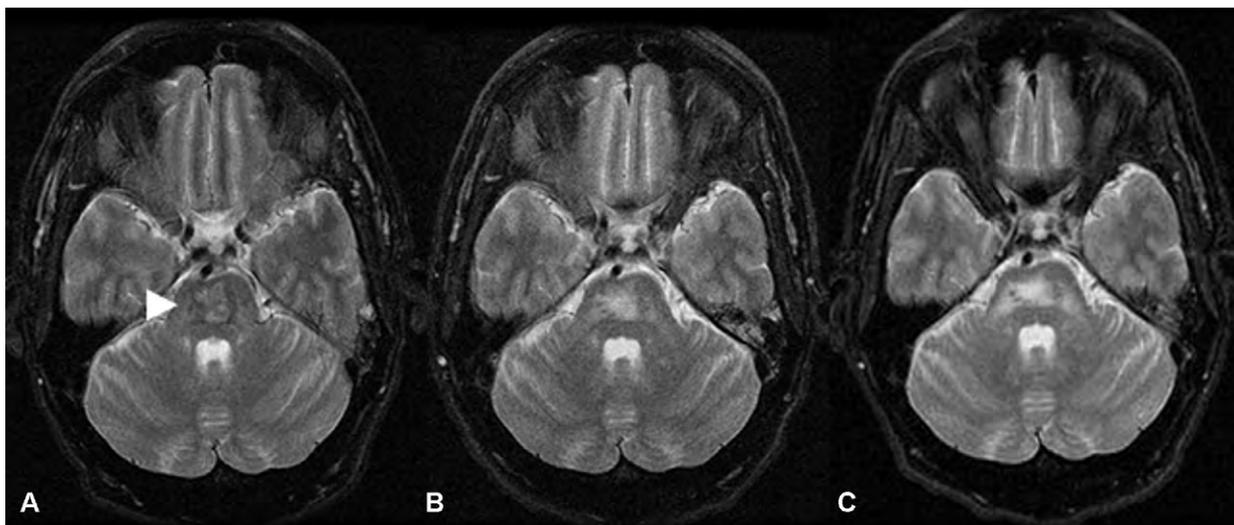
Fig. 23.1. Brain MRI of a 37-year-old insulin-dependent diabetic man with remote kidney transplant, admitted for diabetic ketoacidosis. His calculated serum osmolarity fluctuated from 304 to 287 over a 6 hour period. Serum glucose reached 528 mg/dL (normal, 70–105 mg/dL). The MRI showed a large area of T2-weighted hyperintensity in the pons, with diffusion restriction (not shown), consistent with osmotic demyelination (**A**, arrowhead). Despite symptomatic resolution, serial brain MRI studies obtained at 3 months (**B**) and 1 year after onset (**C**) continued to demonstrate similar imaging abnormalities. Central pontine myelinolysis can develop from rapid serum glucose changes without necessarily any sodium changes.

normovolemic hyponatremia due to SIADH (Decaux et al., 1982). These strategies consist of increasing the daily solute load, which is accomplished by administering urea tablets or by increasing sodium intake, and inhibiting ADH activity. ADH can be inhibited through demeclocycline, a tetracycline derivative, given a dose of 600–1200 mg/day divided into two to four doses per day (Cherrill et al., 1975). The resulting inhibition of the renal response to ADH increases urine output and lowers its osmolality and is referred to as *diabetes insipidus*. Of interest, lithium (used in the treatment of bipolar disorder) can also induce a nephrogenic diabetes insipidus and was used for the treatment of SIADH before demeclocycline was found to be safer and more effective. More recently, arginine vasopressin antagonists, conivaptan and tolvaptan, are a new class of drugs indicated to treat hypervolemic and euvolemic hyponatremia (Ferguson-Myrthil, 2010; Khanna and Menon, 2010). Conivaptan is a nonselective antagonist available intravenously (Ghali et al., 2009), and tolvaptan is a V2-selective arginine vasopressin antagonist available in oral formulation (Aperis and Alivanis, 2011). These drugs produce aquaresis, that is electrolyte-sparing excretion of water, an ideal approach to correct hypervolemic hyponatremia.

HYPERNATREMIA

History and terminology

Hypernatremia refers to a plasma sodium concentration greater than 145 mmol/L. Since sodium is the major contributor to plasma osmolality, hypernatremia is always associated with hyperosmolality (Agrawal et al., 2008). The converse is not true. Hyperosmolality is not always due to hypernatremia but could result from the hyperglycemia of diabetics and the hyperuricemia of renal failure patients. The hypertonic hyperosmolality of hypernatremia causes cellular dehydration due to water shifts following a concentration gradient favoring the extracellular compartment (Ruth and Wassner, 2006).

Clinical findings

Hypernatremia may present with weakness, hyperreflexia, tremor, chorea, or myoclonus in the setting of irritability or frank encephalopathy, which ranges from drowsiness to coma, and may include seizures (Morris-Jones et al., 1967; Sparacio et al., 1976). Extreme ages are most vulnerable. Brain shrinkage induced by hypernatremia can cause rupture of cerebral veins, with focal intracerebral and subarachnoid hemorrhages (Adrogue and Madias, 2000a). Hypernatremia is among the causes of the so-called *reversible splenial lesion syndrome*, a localized cytotoxic edema restricted to the splenium and identified as a nonenhancing T2-weighted and FLAIR hyperintense oval lesion by magnetic resonance imaging (Garcia-Monco et al., 2010). This syndrome has also been reported in association with high-altitude cerebral edema, infectious encephalitis, antiepileptic drug withdrawal, and hypoglycemia (Maeda et al., 2006; Garcia-Monco et al., 2011).

The typical presentation of diabetes insipidus (see below) is a relatively rapid onset of polyuria, polydipsia, and nocturia (Bichet, 2006). Interestingly, patients with neurogenic diabetes insipidus prefer *ice cold water* to satisfy their thirst (Jane et al., 2006).

Laboratory investigations

Hypernatremia can be caused by either a gain of sodium (typically in the setting of hypervolemia) or a loss of water, hypovolemia (Table 23.5) (Agrawal et al., 2008). In the hypervolemic category, after ruling out the more common iatrogenic etiology, the use of hypertonic solutions, it is important to evaluate for the presence of disorders with excess mineralocorticoid activity, such as primary hyperaldosteronism, hyperreninism (renal artery stenosis), and Cushing syndrome. These disorders are suspected in the setting of hypertension, hypokalemia, and/or metabolic alkalosis. In the hypovolemic category, urine is most informative to help distinguish between renal and extrarenal water loss. Renal loss of water causing hypernatremia is either due to osmotic diuresis, where the urine osmolality is high, or diabetes insipidus (DI), in which the urine osmolality is low (Fig. 23.2). In both cases the urine volume is high

(Agrawal et al., 2008). Lithium is one of the most common causes of nephrogenic DI a few months after initiating therapy in as many as 20% of patients with bipolar disorder (Cox and Singer, 1975). Lithium-induced nephrogenic DI may not be reversible (Guirguis and Taylor, 2000). Other causes of nephrogenic DI, which need to be ruled out in the high-volume diluted-urine scenario, include hypercalcemia, hypokalemia, loop diuretics, and sickle cell disease (Khanna, 2006). Extrarenal water loss allows the kidney to both concentrate and decrease production of urine (high urine osmolality, low urine volume). A rare disorder of childhood, idiopathic hypothalamic adipsia is characterized by a complete inability to experience thirst and frequent episodes of hypernatremia (Hayek and Peake, 1982). These patients have a global hypothalamic dysfunction as recognized by obesity, decreased growth hormone-releasing hormone (GHRH), and decreased thyrotropin-releasing hormone (TRH).

Pathophysiology

The symptoms and signs of hypernatremia are due to osmotic shifts of water, whereby water flows out of the intracellular compartment into the relatively hypertonic extracellular compartment. The resulting brain

Table 23.5

Hypernatremia according to volume state

	Hypovolemia		Hypervolemia
Diabetes insipidus Disorders	**Nondiabetes insipidus** • Neurogenic DI Primary and metastatic tumors, tuberculosis, hystiocytosis, sarcoidosis, traumatic brain injury, strokes, encephalitis, Guillain–Barré syndrome • Nephrogenic DI (renal disease or drugs)*	**Gain-of-sodium disorders** Vomiting, diarrhea Nasogastric drainage Enterocutaneous fistula Excessive sweating Burns Osmotic diuresis (hyperglycemia, mannitol, uremia) Hypothalamic adipsia	• Iatrogenic Hypertonic sodium bicarbonate Hypertonic tube feedings/TPN Hypertonic saline solutions Hypertonic dialysis • Excess mineralocorticoid Hyperaldosteronism Cushing's syndrome Hyperreninism
Urine osmolality (Osm), urine volume (UV), and urine sodium (UNa)	Diabetes insipidus: Osm: low UV: high UNa: low	Osmotic diuresis: Osm: high UV: high UNa: low	Osm, UV, UNa: often normal Excess mineralocorticoid: hypertension, hypokalemia, and/or metabolic alkalosis
Treatment	Plasma volume restoration: isotonic saline (0.9% NaCl); oral tap water or D_5W is given to specifically correct hypernatremia. DDAVP in central DI		Diuretics to increase loss of salt and water; D5W can be given to replace urinary water loss

*Nephrogenic diabetes insipidus (DI) can be induced by hypercalcemia, hypokalemia, loop diuretics, lithium, demeclocycline, foscarnet, methoxyflurane, and amphotericin B.

TPN, total parenteral nutrition; DDAVP, desmopressin; D5W, 5% dextrose in water.
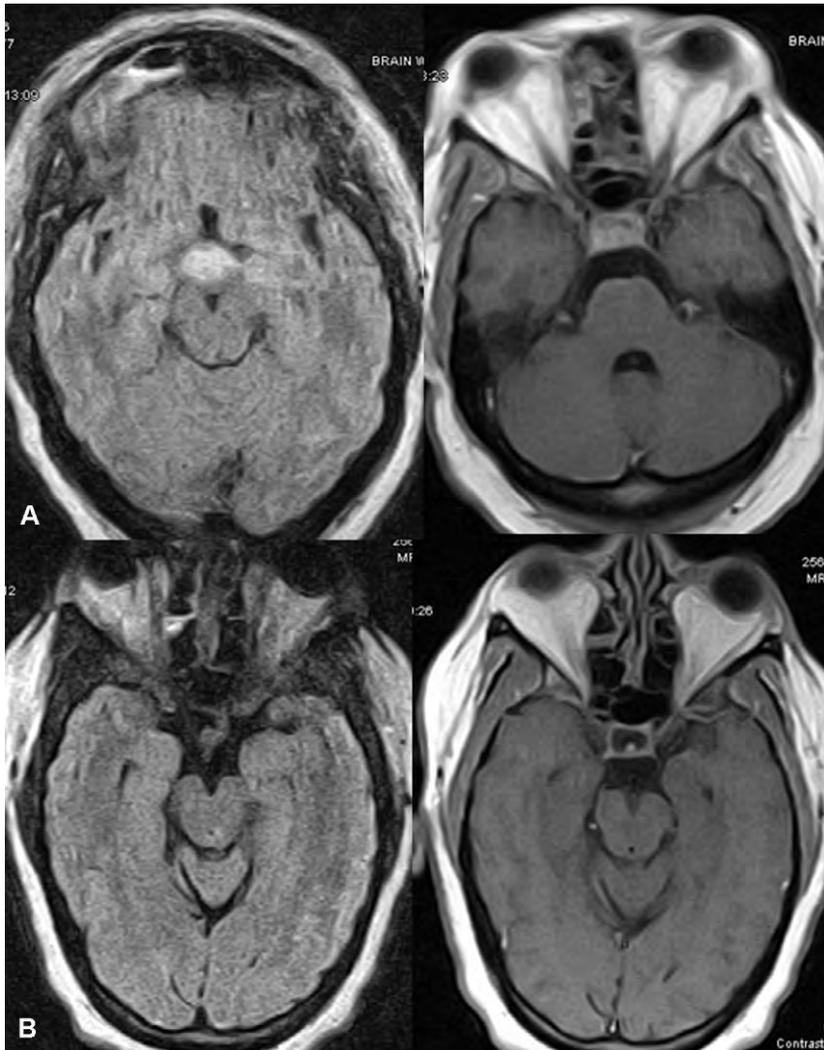
Fig. 23.2. Axial FLAIR (left column) and postcontrast T1-weighted sequences (right column) brain MRI of a 44-year-old woman with pulmonary sarcoidosis and newly developed neurosarcoidosis. The chiasmal contrast-enhanced hyperintensity (**A**) resolved within 1 month after initiating treatment with oral prednisone (**B**). She presented with blurry vision and generalized weakness in the context of excessive thirst and large urinary volume. These features were consistent with diabetes insipidus.

shrinkage can cause hemorrhagic events (intracerebral hemorrhage, subdural hematoma, or subarachnoid hemorrhage in adults; intraventricular hemorrhage in neonates) (Adrogue and Madias, 2000a). The brain adaptive response, or *osmoprotection*, includes the accumulation of electrolytes, sodium, potassium, and chloride (rapid adaptation, hours) as well as organic osmolytes, such as myoinositol, taurine, and glutamine (slow adaptation, after 24–48 hours) (Adrogue and Madias, 2000a). These organic osmolytes are protective against damages to proteins or DNA from increased ion strength within cells.

DI is a disorder characterized by the inability to concentrate urine due to the inability of the hypothalamus to secrete an adequate amount of ADH (neurogenic DI) (Jane et al., 2006) or from a defect in the kidney response to ADH (nephrogenic DI) (Bichet, 2006) (Table 23.5). In both cases, there is excretion of large volumes of diluted urine. Mineralocorticoids cause hypernatremia by stimulating the resorption of sodium and the excretion of potassium at the collecting renal tubules. Aldosterone, the most important mineralocorticoid, is excessively produced in hyperaldosteronism and hyperreninism. Although cortisol has lesser mineralocorticoid activity, such activity is enhanced when the levels become high enough in Cushing's syndrome (Stewart, 1999).

Management

Rapid correction of the hypertonic state may lead to *cerebral edema* (and seizures, coma, and death) as the accumulated electrolytes and solutes cannot be rapidly dissipated (Kang et al., 2002). Slow correction of

hypernatremia (0.5 mmol/L/h or 10 mmol/L/day) is preferred (Adrogue and Madias, 2000a). A rate of 1.5–2.0 mmol/L/h is appropriate in patients with acute symptomatic hypernatremia (Kang et al., 2002). The most important step in the treatment is the calculation of the water deficit, the amount of water that must be administered to return the sodium concentration to normal. The *water deficit* is the difference between the ideal total (iTBW = [sodium] × weight [kg] × [0.5 in men OR 0.4 in women]/140) and the current total body water (cTBW = weight [kg] × [0.5 in men OR 0.4 in women]), as per the formula, in men:

$$([Sodium] \times [weight [kg] \times 0.5]/140) - (weight [kg] \times 0.5)$$

Hypovolemic hypernatremia is treated with isotonic saline until adequate circulation is restored and volume is restored (Hoorn et al., 2008). Often plasma osmolality is concurrently lowered because hypernatremic patients have a plasma osmolality greater than the concentration of isotonic saline (sodium chloride, 154 mmol/L) (Kang et al., 2002). Diuretics are recommended in cases of hypervolemic hypernatremia (Table 23.5).

In cases of central DI, patients respond to DDAVP, a synthetic analog of vasopressin (the human form of ADH), which can be given intranasally (Robinson, 1976). The starting dose is 1–4 µg every 12–24 hours, titrated to reduce urine output to a tolerable level. Overuse of DDAVP can cause plasma overdilution and hyponatremia (iatrogenic SIADH). In cases of nephrogenic DI, the goal of therapy is to remove offending agents (e.g., lithium, demeclocycline, and loop diuretics) and to correct potassium and calcium levels. Lacking these specific targets, a counterintuitive approach in nephrogenic DI is to administer thiazide diuretics in combination with a potassium-sparing diuretic and a salt-restricted diet (Mizuno et al., 2003). The goal is to induce a mild hypovolemia, which triggers the ADH-independent regions of the kidney (mainly the proximal tubule) to increase water resorption and reduce urine output.

HYPOKALEMIA

Terminology

Hypokalemia is defined as a plasma potassium concentration below 3.5 mmol/L. Whereas sodium is the cation of the extracellular space whose shifts affect osmotic movement of water across intra- and extracellular compartments, potassium is 99% intracellular and mostly regulates electrical excitability of muscle and nerve cells (Gennari, 2002). Small changes in plasma potassium can have dramatic consequences. Unlike other electrolyte alterations, hypokalemia or hyperkalemia rarely causes symptoms in the central nervous system. Changes in the extracellular concentration of potassium have predominant effects on the function of the cardiovascular and neuromuscular systems. Severe potassium abnormalities may provoke fatal arrhythmias or muscle paralysis before encephalopathy or seizures may appear (Gennari, 1998).

Clinical findings

Generalized weakness, predominantly proximal, is the common presentation of hypokalemia. from gastrointestinal or renal loss, often induced by drugs. Rhabdomyolysis may develop when the potassium level falls below 3.0 mmol/L. An ascending paralysis with respiratory involvement that spares facial muscles and muscle stretch reflexes occurs when potassium drops under 2.0 mmol/L (Weiss-Guillet et al., 2003). Magnesium deficiency causes reduced intracellular potassium (impaired sodium/potassium-ATPase) and renal potassium wasting. Hypokalemia may also exacerbate digoxin toxicity (Sundar et al., 1983). Non-neurological findings may include heart arrhythmias (with classic EKG findings of flattened T waves, ST segment depression, U waves, and T wave inversion with progressive severity of potassium depletion), rhabdomyolysis, and polyuria. The latter is due to the inability to concentrate urine in hypokalemia, which is a form of *nephrogenic diabetes insipidus*. Of importance, hypokalemia in an otherwise healthy young woman should prompt evaluation for bulimia nervosa. The "compensatory" purging after binge eating in bulimia, aided by self-induced vomiting and abusing laxatives, leads to hyperchloremic metabolic alkalosis and the associated alkalosis-generated hypokalemia. Finally, tetany is seen during alkalosis, which decreases ionized calcium by binding calcium to proteins. Paradoxically, when hypocalcemia is present, hypokalemia protects against tetany. Correction of hypokalemia can precipitate hypocalcemic tetany.

Recurrent, transient attacks of muscle weakness may be seen in *hypokalemic periodic paralysis*, a rare cause of familial hypokalemia. Hypokalemic periodic paralysis type 1, due to a mutation in the calcium channel CACNL1A3 on chromosome 1q, is the most common periodic paralysis, affecting approximately 1 in 100 000 people. This disorder is recognized by transient flaccid weakness in voluntary muscles except facial and respiratory. Attacks may last hours to days and occur upon awakening after vigorous exercise or a carbohydrate-rich meal. If onset is beyond the age of 30 years, thyrotoxicosis, secondary potassium wasting, or medications should be suspected (Table 23.6). Symptoms can be induced by glucose, glucagon, or epinephrine challenges. Permanent proximal weakness eventually develops due to vacuolar myopathy.

Table 23.6

Mechanisms of hypokalemia

Intracellular shift	Increased losses
β_2-sympathomimetics (albuterol, terbutaline, metaproterenol, ephedrine, pseudoephedrine, phenylpropanolamine)	Diuretics (acetazolamide, thiazides, furosemide)
Xanthines (theophylline, caffeine)	Excess mineralocorticoid activity (primary hyperaldosteronism, pseudo-hyperaldosteronism, Cushing's syndrome, high-dose fludrocortisone treatment)
Verapamil intoxication	Nonresorbable anions (diabetic ketoacidosis, vomiting, renal tubular acidosis, toluene, penicillin)
Chloroquine intoxication	
Insulin overdose	
Hypercatecholaminergic states	
Hyperthyroidism	
Hypomagnesemia (potentially caused by cisplatin, aminoglycosides, amphotericin B)	
Familial hypokalemic periodic paralysis	

Laboratory investigations

A variety of conditions related to transcellular shift of potassium or renal/gastrointestinal losses of potassium need to be investigated (Table 23.6). Magnesium and calcium should also be checked as hypomagnesemia-induced hypokalemia and the hypocalcemic hypokalemia of metabolic alkalosis demand correction of magnesium, exclusively, and calcium, preferentially (Siddiqui et al., 1998). Creatine kinase is typically increased when hypokalemia is severe enough to cause rhabdomyolysis (Shintani et al., 1991). Primary hyperaldosteronism is suspected in patients with hypertension, hypokalemia, and a 24 hour urine potassium > 30 mmol/L. Confirmation of the diagnosis requires documenting elevated aldosterone and low renin levels (aldosterone:renin ratio > 30) in the absence of hypovolemia (Vallotton, 1996). Low-dose dexamethasone suppression test is the screening test of choice for patients suspected of having Cushing's syndrome. Morning cortisol level is high because dexamethasone fails to suppress cortisol production in Cushing's syndrome.

Pathophysiology

Potassium regulation is tightly controlled by two systems: intracellular buffering and renal excretion (Gennari, 1998). Cellular redistribution is controlled by the membrane-bound sodium/potassium-ATPase pump, which maintains a high concentration of potassium and a low concentration of sodium inside the cells. Catecholamines, β_2-selective agonists (e.g., albuterol), and insulin decrease potassium by increasing the sodium/potassium-ATPase activity. Hence, hypercatecholaminergic and hyperinsulinergic states commonly cause the transcellular shifts that lead to hypokalemia (Braaten, 1987).

Decreases in plasma hydrogen (which increases pH, induces alkalosis) drive potassium into cells. Thus, the metabolic alkalosis generated from vomiting, hyperaldosteronism, diuretics, and antacid abuse is often associated with hypokalemia (Cely and Contreras, 2001).

Renal potassium excretion is primarily regulated by the mineralocorticoid aldosterone, in part by the same mechanism of increasing the sodium/potassium-ATPase pump activity (Krishnan et al., 2005). Pseudohyperaldosteronism, a syndrome of apparent mineralocorticoid excess (White et al., 1997), is a condition of increased mineralocorticoid activity without elevated aldosterone levels that can be induced by consumption of licorice, a sweet flavor extracted from the root of the legume *Glycyrrhiza glabra* (Fig. 23.3). Licorice contains *glycyrrhetinic acid*, which inhibits the enzyme that deactivates the mineralocorticoid activity of cortisol by transforming into cortisone (11β-hydroxysteroid dehydrogenase), allowing physiologic levels of cortisol to activate the aldosterone receptors in the collecting tubules of the kidney (Schambelan, 1994).

Management

Potassium chloride (KCl) is the most suitable salt for repletion of the common forms of hypokalemia but potassium bicarbonate (KHCO$_3$) and potassium phosphate (KPO$_4$) are used in the setting of associated acidosis and hypophosphatemia, respectively. Potassium replacement should be given at a rate ≤ 20 mEq/h in glucose-free solutions with cardiac monitoring (Gennari, 1998). KPO$_4$ may lead to phosphorus intoxication, which reduces calcium and may lead to hypocalcemic tetany. In hypomagnesemia, magnesium replacement alone should correct hypokalemia. In the hypokalemia associated with alkalotic states, hypocalcemia should be corrected first to avoid the

Fig. 23.3. *Glycyrrhiza glabra*, taken from *Flora von Deutschland, Österreich und der Schweiz*, by Prof. Dr. Otto Wilhelm Thomé, 1885, Gera, Germany. (Permission to use this image granted under GFDL by Kurt Stueber. Source: www.biolib.de, public domain image.)

hypocalcemic tetany that may develop when potassium is corrected alone (Goldfinger, 1969). The hypokalemia of patients with bulimia nervosa should first be addressed by normalizing volume status before potassium replacement can be effective. Whenever present, reduction or removal of offending agents (e.g., albuterol, fludrocortisones, thiazides) may be required. Removal of the dietary product licorice in cases of episodic hypertension and hypokalemia of otherwise unknown etiology should revert the hypokalemia and associated metabolic alkalosis, volume expansion, and hypertension of the licorice-induced pseudohyperaldosteronism (Chatterjee et al., 2010). Patients on treatment with digoxin and diuretics should be monitored for hypokalemia, which causes digitalis toxicity even at low serum digoxin levels (Sundar et al., 1983).

HYPERKALEMIA

Terminology

Hyperkalemia applies to a plasma potassium concentration > 5 mmol/L. Hyperkalemia is a common complication of renal failure. In the absence of renal failure, hyperkalemia is relatively uncommon because the kidneys have the ability to excrete large amounts of potassium.

Clinical findings

The muscle weakness associated with hyperkalemia typically begins in the legs and ascends to the trunk, eventually affecting the arms (McCarty et al., 1998). It is associated with a sensation of burning paresthesias. Even when flaccid quadriplegia with respiratory involvement develops, the cranial nerves are often but not always spared (Cheng et al., 2005; Panichpisal et al., 2010). Hyporeflexia is common. Neurologic deficits without cardiac conduction defects only occur when hypercalcemia (antidysrhythmic) is present. Without this protective element, the most feared non-neurological complication of hyperkalemia is altered cardiac conduction leading to ventricular fibrillation or asystole. The EKG changes include peaked T waves, increased P-R interval, widening of the QRS complex, and loss of the P wave due to the impairment of atrial contraction.

Laboratory investigations

Confirming hyperkalemia requires ruling out hemolysis, leukocytosis, and thrombocytosis, all of which can spuriously elevate the potassium measurement. A small list of conditions related to transcellular shift of potassium or decreased renal losses of potassium need to be investigated (Table 23.7). The major entities to consider are renal failure, metabolic acidosis, insulin deficiency (diabetic ketoacidosis), adrenal insufficiency, crush injuries (rhabdomyolysis), and drugs (potassium-sparing diuretics, NSAIDs, β-blockers, and digoxin intoxication).

Management

In mild hyperkalemia, furosemide is used to enhance excretion. Calcium chloride or calcium gluconate are critical to stabilize cell membranes and prevent cardiac arrhythmias. If severe hyperkalemia is present (e.g., EKG changes, plasma potassium greater than 7.0 mmol/L), calcium should be the first medication administered (Iijima et al., 2005). Calcium chloride is preferred because it provides three times as much calcium but can only be given through a central line. Alkalinizing agents such as sodium bicarbonate are used to shift potassium from the extra- to the intracellular

Table 23.7

Mechanisms of hyperkalemia

Intracellular shift	Decreased renal losses
Tumor lysis syndrome	Renal failure (acute and chronic)
Trauma (rhabdomyolysis)	Hypoaldosteronism (adrenal insufficiency (Addison's disease), hyporeninemic hypoaldosteronism, ACE inhibitors, angiotensin receptor blockers, ciclosporin, NSAIDs)
Hypothermia	
Metabolic acidosis	
Hyperglycemia	
Hypoinsulinemia	Aldosterone resistance (spironolactone, amiloride, triamterene)
β_2-blockers	
Digoxin toxicity	Trimethoprim (high doses)
Hemolysis (pseudohyperkalemia)	Hypovolemia

compartment (Williams, 1992). Sodium bicarbonate 50 mEq given intravenously over 5 minutes decreases plasma potassium by 0.5–1.5 mmol/L within 30 minutes. A complementary strategy is to exploit the ability of insulin to cause the movement of potassium into cells. Insulin is administered with glucose in this situation (Kim, 1996). Nebulizations with the β_2-agonist albuterol can also lower the plasma potassium in a short time frame. However, β_2-agonists may lower the threshold for cardiac arrhythmias and therefore are considered in special circumstances only, bearing the risk in mind. Sodium polystyrene sulfonate (Kayexalate, 20 g given with 100 mL of 20% sorbitol to prevent constipation) and other binding resins promote exchange of potassium for sodium in the gastrointestinal system. Loop diuretics can be used to increase excretion of potassium only if renal function is not impaired.

ACID–BASE DISORDERS

Terminology

Acidemia is defined as an increase in plasma hydrogen concentration above normal, measured by a hydrogen concentration >45 nanoEq/L or a pH below 7.35. *Alkalemia* refers to a decrease in plasma hydrogen concentration below normal, defined by a hydrogen concentration <35 nanoEq/L or a pH above 7.45. The *process* by which the plasma hydrogen concentration increases or decreases is referred to as *acidosis* (low pH) and *alkalosis* (high pH), respectively. A normal acid–base balance rests on the maintenance of pH or acidity, which is kept constant by maintaining the ratio between *bicarbonate* (normal = 24 mmol/L), whose production and excretion is regulated by the kidneys, and *carbon dioxide* (normal $PCO_2 = 40$ mmHg), whose elimination is regulated by the lungs (*Henderson–Hasselbalch* formula) (Maas et al., 1984). If a primary bicarbonate change is not compensated for by a corresponding carbon dioxide change, a *metabolic* acid–base disorder is present. Conversely, if a primary carbon dioxide change is not compensated for by a corresponding bicarbonate change, a *respiratory* acid–base disorder is present. Respiratory acidosis with hypercapnia (elevated PCO_2) is largely due to respiratory insufficiency and respiratory alkalosis with hypocapnia (decreased PCO_2) to any form of hyperventilation. On the other hand, metabolic acidosis may be due to a loss of bicarbonate or an addition of acid, which accumulate anions in plasma other than the major anions, chloride (Cl^-) and bicarbonate (HCO_3^-). The *anion gap*, which is calculated by the difference between sodium, the major plasma cation, and the sum of the major plasma anions ($Na^+ - [Cl^- + HCO_3^-]$), can distinguish a metabolic acidosis due to the loss of bicarbonate (*nonanion gap metabolic acidosis* or *hyperchloremic acidosis*; gap <12 mEq), largely due to gastrointestinal losses, versus that resulting from the addition of acid (*anion gap acidosis*; gap > 12 mEq) (Kraut and Madias, 2010). The latter can be caused by lactic acidosis, ketoacidosis, uremia, and toxic ingestions (paraldehyde, methanol, ethylene glycol, and salicylate poisoning, among others) (Table 23.8).

Clinical findings

Acidotic or alkalotic states present neurologically with alterations in the level of consciousness which may include epileptic activity and can rapidly progress to coma if the underlying disorder is left unchecked. Tachypnea-associated *respiratory alkalosis* tends to cause lightheadedness, syncope, or seizures from reduced cerebral blood flow (see section on pathophysiology) but also peripheral symptoms such as acral and circumoral paresthesias and muscle cramps, with hyperreflexia and sometimes Chvostek's sign on examination (Saltzman et al., 1963). The term *central neurogenic hyperventilation* has been applied to describe the progressive tachypnea causing hypocapnia and respiratory

Table 23.8

Selected causes of anion-gap and nongap metabolic acidosis

Anion-gap metabolic acidosis	Decreased renal losses
Diabetic ketoacidosis	Gastrointestinal (diarrhea, intestinal fistula, pancreatic shunt/ileostomy)
Alcoholic ketoacidosis	
Lactic acidosis	Renal tubular acidosis
Uremia	Multiple myeloma or other causes of hyperparaproteinemia
Toxins (methanol, paraldehyde, ethylene glycol, ammonium chloride)	Medications (carbonic anhydrase inhibitors, lithium toxicity)
Medications (salicylates, isoniazid, excessive iron, metformin)	

alkalosis in patients with a range of pontine lesions, including tumors, infections, demyelination, and strokes (Gottlieb et al., 1987; Shahar et al., 2004; Nystad et al., 2007; Takahashi et al., 2007). *Respiratory acidosis* from hypoventilation can be a complication of, among other possible causes, brainstem injury, diaphragmatic paralysis, sleep apnea, amyotrophic lateral sclerosis, and Guillain–Barré syndrome, conditions whose recognition is aided by other, more specific clinical features. In all hypoventilation syndromes, once the PCO_2 rises above 50 mmHg, the syndrome of intracranial hypertension develops due to increased cerebral vasodilation (Jennum and Borgesen, 1989; Kirkpatrick et al., 1994; Hayward and Gonsalez, 2005). Symptoms secondary to increased intracranial pressure include nocturnal or early morning headaches, disorientation, and visual disturbances ranging from blurry vision to blindness (Quinn et al., 2008). Signs of intracranial hypertension include papilledema, optic atrophy, and, in severe cases, pupillary changes or upper motor neuron findings suggestive of herniation syndromes (Reeve et al., 1985). In *metabolic acidosis*, decompensation or first presentations of diabetes or renal failure need to be sought. Signs and symptoms of raised intracranial pressure occur less often in metabolic compared to respiratory acidosis. Distinct clinical syndromes with visual presentations have been described for two of the anion gap metabolic acidoses. *Methanol toxicity* is a severe form of anion gap acidosis which develops among those who accidentally ingest windshield wiper fluid or household cleaners. Methanol is converted into formaldehyde and formic acid, which are directly toxic to the retina (Treichel et al., 2004). The full picture consists of epileptic encephalopathy with unreactive mydriasis and large symmetrical central scotomas due to retinal ganglion cell destruction. Infarcts or hemorrhage in the putamen are characteristic MRI findings (Faris et al., 2000; Bhatia et al., 2008). *Ethylene glycol toxicity* is an anion gap acidosis that results from ingestion of automotive antifreeze and hydraulic brake fluids. Ethylene glycol is converted into glycolic and oxalic acid, which are preferentially toxic to the optic nerve and may cause optic neuropathy, seizures, and coma in the setting of hypocalcemia, oxaluria (oxalate crystals), and renal failure (Lloyd and Fraunfelder, 2007). Unlike methanol, the visual syndrome of ethylene glycol poisoning tends to affect the thalamus and brainstem rather than the putamen (Hantson and Duprez, 2006; Sharma et al., 2009).

Laboratory investigations

Arterial blood gases are critical to ascertaining pH and bicarbonate levels and determining whether a metabolic or respiratory acid-based disorder is present, with or without respiratory or metabolic compensation, respectively. Hypophosphatemia is a typical accompaniment of respiratory alkalosis, which causes rapid shift of phosphate from the extracellular to the intracellular compartment (Datta and Stone, 2009). Potassium and chloride may also be low.

Pathophysiology

A decrease in brain pH causes vasodilation, which increases cerebral blood flow. An increase in brain pH causes vasoconstriction, which decreases cerebral blood flow. Unlike oxygen, carbon dioxide, which can easily and rapidly cross the blood–brain barrier, affects cerebral blood flow. Conversely, bicarbonate does not cross the blood–brain barrier. Hence, respiratory but not metabolic acid–base disorders can have large effects on cerebral blood flow. An increase in brain pH caused by respiratory alkalosis (hyperventilation) can cause marked reduction in cerebral blood flow, a principle which has been incorporated to the treatment of intracranial hypertension, alongside head elevation and hyperosmolar therapy with mannitol or hypertonic saline (Singhi and Tiwari, 2009).

Management

The correction of hypercapnia in respiratory acidosis should be made gradually since rapid clearance of CO_2 may not allow enough time for the excretion of

compensatory bicarbonate. The resulting metabolic alkalosis may lead to seizures (Faden, 1976). Also, there should be cautious oxygen therapy to avoid suppressing the hypoxic drive for respiration and resulting CO_2 retention. In cases of methanol toxicity, administration of ethanol, a competitive substrate of alcohol dehydrogenase, may have some benefit in reducing the formation of formic acid (Pappas and Silverman, 1982). Ethanol (alcohol) can be given intravenously or by mouth and blood-alcohol levels should be kept between 100 and 200 mg/dL. Activated charcoal may also be given to trap methanol in the gastrointestinal tract (Mathangi et al., 1995). Fomepizole (Antizol), a selective inhibitor of alcohol dehydrogenase, is effective in the treatment of both ethylene glycol and methanol poisoning (Brent, 2009). An infusion of 15 mg/kg intravenous bolus is followed by 10 mg/kg intravenously every 12 hours for four doses or until the ethylene glycol or methanol level is <20 mg/dL and the patient is asymptomatic. If the source of metabolic acidosis cannot be identified, patients may require sodium bicarbonate (if the concentration is <8 mmol/L) and intubation to assist with respiratory compensation via hyperventilation.

The treatment of diabetic ketoacidosis (DKA) presents a particular challenge, as the disorder is associated with depletion in total body potassium, but increased plasma potassium because of the lack of insulin. Treatment with insulin moves potassium into cells causing hypokalemia. If a patient with DKA manifests hypokalemia at presentation, potassium depletion is severe. In this situation, potassium should be replaced prior to initiating insulin therapy (Wallace and Matthews, 2004).

Specific treatment for alkalosis is typically not necessary. In the case of respiratory alkalosis causing lightheadedness, cramps, or paresthesias, patients can breathe into a brown paper bag as a simple and effective method to raise PCO_2 and lower the pH (Jozefowicz, 1989).

OTHER ELECTROLYTIC DISTURBANCES

Hypocalcemia

Most often asymptomatic, hypocalcemia can induce both peripheral and central nervous system manifestations. The former can range from finger paresthesias and perioral numbness, to *tetany* and trismus, to *opisthotonos* and respiratory compromise (Riggs, 2002). Tetany refers to painful finger contractions resulting in thumb adduction, metacarpophalangeal flexion, and interphalangeal finger extension, which may be confused with dystonia (Fig. 23.4). Besides hypocalcemia, tetany may also be seen in hypomagnesemia and both metabolic (hypokalemic) and respiratory alkalosis. The central nervous system involvement manifests as encephalopathy

Fig. 23.4. Intermittent painful hand posturing, typical of tetany, in a 66-year-old diabetic seamstress. While sewing a button, she noted the sudden onset of left thumb adduction and index finger extension, which was painful and lasted about 5 minutes. In the subsequent 6 months, she had several additional episodes, eventually without triggers. Evaluation demonstrated early, previously unrecognized, renal insufficiency and hypocalcemia.

with seizures due to intracranial hypertension. *Chvostek's sign* (facial contraction after facial nerve percussion) and *Trousseau's sign* (tetany induced by inflating the blood pressure cuff 20 mmHg above systolic pressure) are helpful signs demonstrating hypocalcemia-induced peripheral nerve irritability (Athappan and Ariyamuthu, 2009). Hypoparathyroidism is the most common cause of hypocalcemia and often develops as a complication of thyroid surgery or radical resection of head and neck cancers (Shoback, 2008). It is confirmed when the parathyroid hormone (PTH) is low or inappropriately normal. Chronic hypoparathyroidism may express with *basal ganglia calcifications* (Narayan et al., 2008). Low calcium stimulates PTH secretion (secondary hyperparathyroidism), leading to hypophosphatemia. If PTH is high, serum phosphorus should be checked next: if low, *vitamin D deficiency or resistance* (rickets) is suspected; if phosphorus is high, *pseudohypoparathyroidism* (sporadic or autosomal-dominant (Albright's osteodystrophy)), rhabdomyolysis, tumor lysis syndrome, renal insufficiency, and phosphate ingestion must be investigated (Moe, 2008). Severe hypermagnesemia (>6 mg/dL) can lead to hypocalcemia by inhibiting PTH secretion. Other causes of hypocalcemia are acute pancreatitis, hypoalbuminemia, and such drugs as phenobarbital, alcohol, phenytoin, carbamazepine, foscarnet, cimetidine, and aluminum. Pseudohypocalcemia can be seen with heparin, oxalate, citrate, or hyperbilirubinemia. *Hypoalbuminemia* may falsely normalize calcium levels, which will need to be corrected (corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.4 − serum albumin [g/dL]).

Patients with acute symptomatic hypocalcemia (calcium level lower than 7.0 mg/dL, ionized calcium level lower than 0.8 mmol/L) should be treated promptly with intravenous calcium. Calcium gluconate is preferred

over calcium chloride because it causes less tissue necrosis if extravasated. Calcium gluconate 10–30 mL of 10% given intravenously can be administered over 10 minutes. After 2 hours, continuous intravenous infusion should be started if the ionized calcium level is low, at 0.5 mg/kg/h (moderate) or 1–1.5 mg/kg/h (severe hypocalcemia) (Dickerson, 2007). The potassium-sparing spironolactone has been used in patients with renal wasting of calcium and magnesium (Al-Gharabally et al., 2002). Calcium administration may precipitate digitalis toxicity in patients on digoxin whose digitalis levels are high. When *hypomagnesemia* is present concurrently, magnesium should be replaced before calcium, and the underlying cause of the low magnesium explored (in the presence of metabolic acidosis, conversely, calcium must be corrected before correcting the acidosis) (Moe, 2008).

Hypercalcemia

Hypercalcemia is reported as elevation of total plasma calcium levels rather than ionized calcium levels. Since approximately 50% of total calcium is protein-bound, pseudohypercalcemia is documented in some patients with hyperalbuminemia and multiple myeloma. Hypercalcemia may be asymptomatic or manifest as depression or anxiety, or as encephalopathy ranging from drowsiness to visual loss, to seizures and coma (Kastrup et al., 2002). Parkinsonism has been reported in the setting of hyperparathyroidism (Kovacs et al., 1993). Proximal weakness and hyperreflexia can be features of chronic hypercalcemia. The usual etiologies are primary hyperparathyroidism, hyperthyroidism, malignancy, sarcoidosis, adrenal insufficiency, and vitamin D intoxication. Drugs capable of increasing calcium are thiazides, calcium carbonate (antacid), lithium, and theophylline. Treatment is based on the use of bisphosphonates (pamidronate, etidronate) to prevent osteoclast recruitment and viability and calcitonin, which inhibits bone resorption and enhances calcium excretion (Pecherstorfer et al., 2003). Furosemide for the treatment of hypercalcemia should be restricted among those with heart failure, as it can foster release of calcium from bone, thus worsening hypercalcemia.

Hypomagnesemia

Mainly an intracellular electrolyte, the serum magnesium level is not a reliable way to determine total body magnesium depletion. Tetany with Chvostek's and Trousseau's signs occurs either directly in hypomagnesemia or by reducing ionized calcium levels (Siddiqui et al., 1998). Central nervous system involvement includes seizures, confusion, delirium, or coma. Hyperreflexia, tremor, chorea, and startle responses with myoclonus

have been described (Flink, 1985; Cohen and Kitzes, 1987). Common etiologies are parenteral nutrition, acute tubular necrosis, hypoparathyroidism, hyperthyroidism, and hyperaldosteronism.

Hypermagnesemia

Weakness and hyporeflexia are seen at levels of between 7 and 9 mmol/L and areflexia and parasympathetic blockade are the hallmark of magnesium >9 mmol/L. The decreased neuromuscular excitability is due to displacement of calcium by magnesium at the neuromuscular junction (Krendel, 1990). Respiratory failure is a potential development. There is no central nervous system involvement, confirmed by the lack of epileptic or cognitive symptoms. However, in severe hypermagnesemia the fixed and dilated pupils, resulting from parasympathetic blockade, and the neuromuscular blockade may mimic a brainstem herniation syndrome and cause a pseudocomatose state (Rizzo et al., 1993). Iatrogenic magnesium, contained in antacids and laxatives or given during the treatment of eclampsia, is required for the neurologic deficits to appear (Touyz, 2004). Other disorders that can cause hypermagnesemia include diabetic ketoacidosis, adrenal insufficiency, hyperparathyroidism, and lithium intoxication. Hypermagnesemia may worsen neuromuscular diseases such as Lambert–Eaton myasthenic syndrome and myasthenia gravis (Bashuk and Krendel, 1990).

Hypophosphatemia

Peripheral neurologic symptoms of hypophosphatemia begin when the levels fall below 1 mg/dL (*acute areflexic paralysis* with diaphragmatic, pharyngeal, facial, and extraocular weakness preceded by perioral paresthesias) and central nervous system deficits appear when phosphate < 0.5 mg/dL (Jansen and Velkeniers, 2003). Hypophosphatemic encephalopathy can mimic Wernicke's encephalopathy, with seizures, tremor, ataxia, nystagmus, and bilateral abducens palsy (Vanneste and Hage, 1986). Myopathy develops due to myonecrosis and subsequent rhabdomyolysis. More commonly iatrogenic, as is the case with hypermagnesemia, low phosphate may develop in the setting of hyperalimentation, hemodialysis, hyperparathyroidism, respiratory alkalosis, aluminum-containing antacids, and glucose load in alcoholic or starved patients.

Hyperphosphatemia

Hyperphosphatemia is invariably associated with the clinical features of hypocalcemia (Matustik, 1986). Other pathways leading to hypocalcemia are summarized in Figure 23.5.
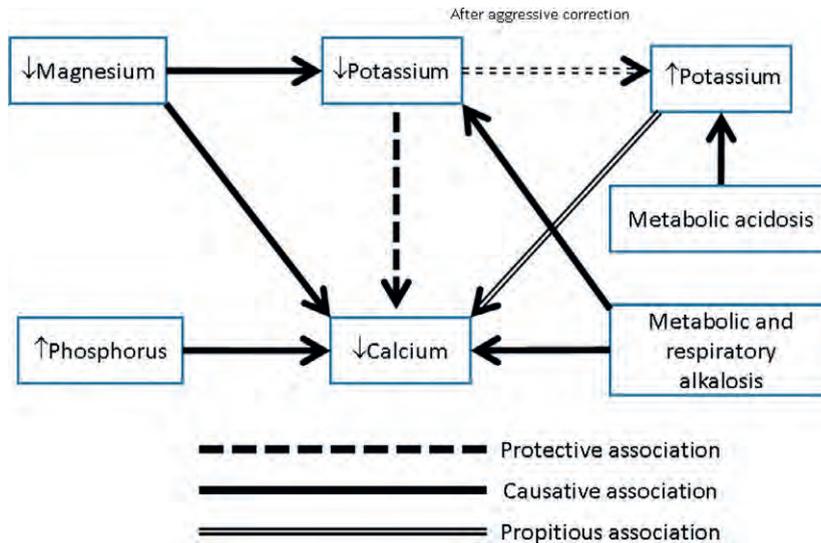
Fig. 23.5. Electrolytic abnormalities converging in hypocalcemia. Hypomagnesemia contributes to hypokalemia due to impaired membrane ATPase and urinary losses of potassium. Hypomagnesemia causes hypocalcemia for unclear reasons (decreased PTH levels and end organ resistance to PTH and/or alterations in vitamin D metabolism). Hyperchloremic metabolic alkalosis and the associated alkalosis-generated hypokalemia resulting from vomiting, for instance, may induce hypocalcemia directly or through the generation of hypokalemia. Some or all of the clinical manifestations seen in hypokalemia, hypomagnesemia, and hyperphosphatemia, as well as in alkalotic states, may result from the resulting hypocalcemia.

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