extracellular K^+ can cause significant hypo- or hyperkalemia. Insulin, β_2-adrenergic activity, thyroid hormone, and alkalosis promote cellular uptake of K^+ by multiple interrelated mechanisms, leading to hypokalemia. In particular, alterations in the activity of the endogenous sympathetic nervous system can cause hypokalemia in several settings, including alcohol withdrawal, hyperthyroidism, acute myocardial infarction, and severe head injury.

Weakness is common in severe hypokalemia; hypokalemia causes hyperpolarization of muscle, thereby impairing the capacity to depolarize and contract. In this particular patient, Graves' disease caused hyperthyroidism and hypokalemic paralysis (thyrotoxic periodic paralysis [TPP]). TPP develops more frequently in patients of Asian or Hispanic origin. This predisposition has been linked to genetic variation in Kir2.6, a muscle-specific, thyroid hormone–induced K^+ channel; however, the pathophysiologic mechanisms that link dysfunction of this ion channel to TPP have yet to be elucidated. The hypokalemia in TPP is attributed to both direct and indirect activation of the Na^+/K^+-ATPase by thyroid hormone, resulting in increased uptake of K^+ by muscle and other tissues. Thyroid hormone induces expression of multiple subunits of the Na^+/K^+-ATPase in skeletal muscle, increasing the capacity for uptake of K^+; hyperthyroid increases in β-adrenergic activity are also thought to play an important role in TPP.

Clinically, patients with TPP present with weakness of the extremities and limb girdle, with paralytic episodes that occur most frequently between 1 and 6 AM. Precipitants of weakness include high carbohydrate loads and strenuous exercise. Signs and symptoms of hyperthyroidism are not always present, often leading to delays in diagnosis. Hypokalemia is often profound and usually accompanied by redistributive hypophosphatemia, as in this case. A TTKG of <2–3 separates patients with TPP from those with hypokalemia due to renal potassium wasting, who will have TTKG values that are >4. This distinction is of considerable importance for therapy; patients with large potassium deficits require aggressive repletion with K^+-Cl^-, which has a significant risk of rebound hyperkalemia in TPP and related disorders.

APPROACH TO MANAGEMENT

Ultimately, definitive therapy for TPP requires treatment of the associated hyperthyroidism. In the short term, however, potassium replacement is necessary to hasten muscle recovery and prevent cardiac arrhythmias. The average recovery time of an acute attack is reduced by ~50% in patients treated with intravenous K^+-Cl^- at a rate of 10 meq/h; however, this incurs a significant risk of rebound hyperkalemia, with up to 70% developing a plasma K^+ concentration of >5.0 meq/L. This potential for rebound hyperkalemia is a general problem in the management of all causes of redistributive hypokalemia, resulting in the need to distinguish these patients accurately and rapidly from those with a large K^+ deficit due to renal or extrarenal loss of K^+. An attractive alternative to K^+-Cl^- replacement in TPP is treatment with high-dose propranolol (3 mg/kg), which rapidly reverses the associated hypokalemia, hypophosphatemia, and paralysis. Notably, rebound hyperkalemia is not associated with this treatment.

CASE 8

A 66-year-old man was admitted to hospital with a plasma K^+ concentration of 1.7 meq/L and profound weakness. The patient had noted progressive weakness over several days, to the point that he was unable to rise from bed. Past medical history was notable for small-cell lung cancer with metastases to brain, liver, and adrenals. The patient had been treated with one cycle of cisplatin/etoposide 1 year before this admission, which was complicated by acute kidney injury (peak creatinine of 5, with residual chronic kidney disease), and three subsequent cycles of cyclophosphamide/doxorubicin/vincristine, in addition to 15 treatments with whole-brain radiation.

On physical examination, the patient was jaundiced. Blood pressure was 130/70 mmHg, increasing to 160/98 mmHg after 1 L of saline, with a JVP at 8 cm. There was generalized muscle weakness.

Laboratory Data	2 Months PTA	Admission	HD2	Units
Sodium	143	149	144	meq/L
Potassium	3.7	1.7	3.5	meq/L
Chloride	103	84	96	meq/L
Bicarbonate	26	44	34	meq/L
Venous pH		7.47		pH
Venous P_{CO_2}		62		mmHg
BUN	21	41	40	mg/dL
Creatinine	2.8	2.9	2.3	mg/dL
Magnesium	1.3	1.6	2.4	mg/dL
CPK		183		U/L
ALT	8	75		U/L
Albumin	3.4	2.8	2.3	
Adjusted anion gap	15	24	18	
Total bilirubin	0.65	5.19		mg/dL
Alkaline phosphatase	93	217		U/L
Urine sodium		35	28	meq/L
Urine potassium		25	49	meq/L
Urine chloride		48	51	meq/L
Urine osmolality		391		mOsm/kg
Plasma osmolality		312		mOsm/kg
Urine pH		5.5		
Plasma ACTH		185		pg/mL (7–50 pg/mL)
Plasma cortisol		94		pg/mL (3–16 pg/mL)
24-h urine cortisol		1044		μg/24 h (4–50 μg/24 h)

Abbreviations: ACTH, adrenocorticotropic hormone; HD2, hospital day 2; PTA, prior to admission.

The patient's hospital course was complicated by acute respiratory failure attributed to pulmonary embolism; he died 2 weeks after admission.

APPROACH TO DIAGNOSIS

Why was this patient hypokalemic? Why was he weak? Why did he have an alkalosis?

This patient suffered from metastatic small-cell lung cancer, which was persistent despite several rounds of chemotherapy and radiotherapy. He presented with profound hypokalemia, alkalosis, hypertension, severe weakness, jaundice, and worsening liver function tests.

With respect to the hypokalemia, there was no evident cause of nonrenal potassium loss, e.g., diarrhea. The urinary TTKG was 11.7, at a plasma K^+ concentration of 1.7 meq/L; this TTKG value is consistent with inappropriate renal K^+ secretion, despite severe hypokalemia. The TTKG is calculated as $(P_{osmol} \times U_{Potassium})/(P_{Potassium} \times U_{osmol})$. The expected values for the TTKG are <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia (see also Case 2 and Case 6).

The patient had several explanations for excessive renal loss of potassium. First, he had had a history of cisplatin-associated acute kidney injury, with residual chronic kidney disease. Cisplatin can cause persistent renal tubular defects, with prominent hypokalemia and hypomagnesemia; however, this patient had not previously required potassium or magnesium repletion, suggesting that cisplatin-associated renal tubular defects did not play a major role in this presentation with severe hypokalemia. Second, he was hypomagnesemic on presentation, suggesting total-body magnesium depletion. Magnesium depletion has inhibitory effects on muscle Na^+/K^+-ATPase activity, reducing influx into muscle cells and causing a secondary increase in K^+ excretion. Magnesium depletion also increases K^+ secretion by the distal nephron; this is attributed to a reduction in the magnesium-dependent, intracellular block of K^+ efflux through the secretory K^+ channel of principal cells (ROMK, Fig. 64e-1). Clinically, hypomagnesemic patients are