Difficulty Getting Up In the Morning: A Case of Thyrotoxic Periodic Paralysis

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Learning Objective 1: Recognize thyrotoxic periodic paralysis as an uncommon complication of thyrotoxicosis

Learning Objective 2: Treat thyrotoxic periodic paralysis with nonselective beta blockade and cautious potassium supplementation

Case: A 47 year old man of Eastern European descent was brought to the emergency department after awakening with profound muscle weakness. He got out of bed at 6:00 am, but was so weak he fell to the floor and was unable to get up. After some time, he pulled his phone to the floor and called emergency medical services. He had noticed some mild myalgias in his right thigh the previous night, but had no other recent symptoms. On exam, he was afebrile, heart rate was 90 beats per minute and blood pressure 160/94 mmHg. He had flaccid proximal quadriparesis and diffuse mildly-diminished reflexes. Mental status, sensation, speech, and cranial nerves were normal. He denied recent exertion, high carbohydrate intake, or stimulant use. However, he did admit to being under significant stress related to personal life events. Labs revealed severe hypokalemia of 1.7 mmol/L and subsequent ECG showed associated changes. Further investigation revealed an undetectable thyroid stimulating hormone and a moderately elevated free thyroxine value of 2.2 ng/dL. Other labs were unremarkable. He did not present with obvious symptoms of hyperthyroidism, but in retrospect did recall recent episodes of loose stool, fine hand tremors, and palpitations over the preceding months. Thyrotoxic periodic paralysis was diagnosed and the patient was admitted overnight for close monitoring. After receiving propranolol and gentle potassium repletion the hypokalemia resolved, the muscle weakness improved dramatically, and the ECG normalized. Prior to discharge, he was started on methimazole and beta blockade. As an outpatient, he was later diagnosed with Grave's disease.

Discussion: Thyrotoxic periodic paralysis (TPP) is a well-described complication of hyperthyroidism. It is relatively common in patients of Asian lineage. However, it remains quite rare in other races. Patients tend to be young adult men presenting with flaccid paralysis that progresses from the lower to the upper extremities. Sensation is unaffected. Patients most often present early in the morning after an overnight onset. The event is often preceded by high carbohydrate intake, alcohol intake, or strenuous exercise. This patient's attack seems instead to have been precipitated by personal life stress, suggesting a common pathway involving glucocorticoid and insulin excess. It is thought that the excess thyroxine simultaneously increases the adrenergic response, the activity of the Na+/K+-ATPase pumps and insulin release, all of which shift potassium ions intracellularly. The functional hypokalemia causes hyperpolarization of the motor neurons leading to paralysis. Neither the severity, duration, nor the etiology of the hyperthyroidism are correlated with TPP. When treating TPP, total body stores of potassium are not decreased and overaggressive potassium repletion can be fatal. Potassium repletion is, however, important in prevention of fatal hypokalemic arrhythmias in the acute setting. Ongoing supplementation for prophylaxis against attacks is not helpful. Administration of a non-selective beta blocker may be as useful as potassium chloride administration and is without the risk of rebound hyperkalemia. These should be taken until the patient reaches a euthyroid state and definitive treatment for hyperthyroidism is completed.

Isolated Pulmonary Anti-GBM disease

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Learning Objective 1: Although Anti-GBM disease usually involves the kidneys, it might very rarely presents exclusively in lungs

Learning Objective 2: Early recognition and treatment of Anti-GBM disease might delay or prevent renal involvement

Case: A 30-year-old Caucasian lady presented to the hospital with severe dyspnea that started one week after exposure to smoke from burning leaves. The dyspnea progressively worsened until she became symptomatic at rest prior to presentation. It was associated with non-productive cough but not chest pain, paroxysmal nocturnal dyspnea, orthopnea, hemoptysis, wheezing, or fever. Her past medical history was negative for lung disease. She was not taking any medications. Social history was significant for 2 packs per day cigarette smoking.

In the emergency room, she quickly progressed to hypoxemic respiratory failure requiring intubation and mechanical ventilation. Initial chest X-ray revealed alveolar infiltrates and she was diagnosed with acute pulmonary edema. She was treated with diuretics but became hypotensive and oliguric. She was also started on empirical antibiotics for possible pneumonia. The lack of response in the next 72 hours prompted discontinuation of antibiotics, and flexible bronchoscopy suggested alveolar hemorrhage. At this point, the patient developed renal failure requiring hemodialysis. Infectious and rheumatological work up was negative and anti-glomerular basement membrane (anti-GBM) antibodies were found to be strongly positive. There was a concern that renal failure might be secondary to anti-GBM disease. The patient was started on high dose steroids on day 5. Since the patient was too unstable to undergo kidney biopsy, plasmapheresis was given empirically for 14 days. Oxygenation improved, and the patient was extubated on day 9. Subsequently, kidney biopsy was performed that revealed acute tubular necrosis but not anti-GBM disease. The patient resumed urinating after three weeks, and creatinine improved to almost normal prior to discharge.

Discussion: Anti-GBM disease is a rare autoimmune disease with an annual incidence of 0.5 cases per million in the general population. The disease is secondary to anti-GBM antibodies against the noncollagenous 1 domain of the alpha 3 chain of type IV collagen found in the glomerular basement membrane. The disease manifests in type IV collagen-rich organs such as kidney (anti-GBM glomerulonephritis) and lungs (Goodpasture's disease). Very rarely, it may only present in the lungs, as in our case. Isolated pulmonary anti-GBM disease has been reported in the literature. Renal involvement might be absent, subtle, or eventually develop months to years from initial presentation. The inciting event is usually environmental exposure to inhalational toxins, representing an environmental trigger in a genetically predisposed individual. It was hypothesized that early recognition and treatment prevented overt renal involvement in our patient.

Alveolar hemorrhage is an important differential diagnosis of alveolar infiltrates on chest X-ray and should prompt a physician to check for anti–GBM antibodies in a patient without a clear etiology for ARDS, pneumonia, or pulmonary edema. Timely diagnosis and treatment could be life-saving.

Follow up is essential in patients with isolated pulmonary anti-GBM disease. Recurrence is common and can occur months to years after the initial presentation as an isolated pulmonary disease or with frank pulmonary-renal syndrome.

Running on Empty

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Learning Objective 1: Recognize anemia as an important cause of heart failure.
Learning Objective 2: Understand the pathophysiology of anemia-induced high output heart failure.

Case: A 43 year-old woman with a history of menorrhagia presented with three weeks of progressively worsening shortness of breath and lower extremity swelling. She had a heart rate of 120 beats per minute and conjunctival pallor. Her jugular venous pressure was elevated, and she had an enlarged, laterally displaced PMI. There was lower extremity pitting edema extending up to the thighs bilaterally. There was four chamber dilatation by echocardiography, with an ejection fraction of 60%. The initial hemoglobin level was 2.5 g/dL, and the mean corpuscular volume was 47.2 fL. Results of iron studies revealed severe iron-deficiency anemia, with an iron level of 13 ng/mL, total iron-binding capacity of 410 ng/mL, percent iron saturation of 3%, and ferritin of 5 ng/mL. After 2 units of packed red blood cells and several days of intravenous Furosemide, she had improvement of her symptoms.

Discussion: Heart failure is among the most common conditions that an internist treats, but the diagnosis is not always secondary to structural heart disease. Typically, patients with heart failure have either systolic or diastolic dysfunction with a low or normal cardiac output, respectively. However, in some cases the resting cardiac index is elevated beyond the normal range of 2.5 to 4.0 L/min per m2. A number of disorders can lead to a rise in cardiac output resulting in high output heart failure, and iron deficiency anemia is an important cause. Other conditions that can lead to high output heart failure include sepsis, systemic arteriovenous fistulas, thyrotoxicosis, beriberi, multiple myeloma, obesity, pregnancy, and carcinoid syndrome. Several characteristic findings are usually seen on physical examination in patients with high output heart failure. The pulse pressure is typically wide, and the pulse is usually bounding with a quick upstroke. Pistol-shot sounds auscultated over the femoral arteries and a systolic bruit heard over the carotid arteries are both highly suggestive of elevated left ventricular stroke volume due to a hyperdynamic state. In high output heart failure, patients typically have warm rather than cold extremities due to low systemic vascular resistance and peripheral vasodilation. Patients with chronic high output may develop signs of pulmonary and systemic congestion associated with low output heart failure, including raised jugular venous pressure, pulmonary rales, and peripheral edema. Only in cases of severe anemia (hemoglobin less than 5 g/dL) does heart failure develop in the absence of underlying heart disease. Although the mechanism is not completely understood, it is postulated that anemia can cause peripheral vasodilation through increased renal and vascular nitric oxide production. This, in turn, causes low systemic vascular resistance. Severe anemia also results in reduced serum viscosity. Ineffective blood pressure and volume leads to chronic activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and increased serum vasopressin concentrations. Over time, chronic volume overload and increased stroke volume gradually cause ventricular enlargement, remodeling, and heart failure. Clinicians should be able to recognize the signs and symptoms of high output heart failure, as it is often associated with a potentially reversible etiology.

Spontaneous Pneumothorax: The Gateway to a Unique Clinical Entity

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Learning Objective 1: Recognize the numerous clinical and radiologic manifestations of tuberous sclerosis

Learning Objective 2: Recognize that Sirolimus is a new ground-breaking treatment for certain manifestations of tuberous sclerosis

CASE: A 27 year old woman with PMH of a seizure disorder presented to the ED complaining of sudden onset chest pain and DOE. The physical exam was significant for decreased breath sounds over the left lung, multiple facial lesions over her bilateral cheeks and nasal bridge, hypopigmentation of her arms, and pitting of her nails. The CXR revealed a left sided pneumothorax, and the CT demonstrated mixed solid and fat containing lesions suspicious for pulmonary lymphangioleiomyomatosis and large renal angiomyolipomas. Taken together, the history, exam and radiologic findings were suspicious for tuberous sclerosis, and a brain MRI further revealed multiple cortical and subcortical tubers, numerous subependymal nodules, and a white matter hamartoma. To provide a complete assessment of this condition, the patient was referred for Ophthalmic examination, which identified bilateral retinal hamartomas. This constitution of clinical findings, along with her history of seizure disorder and facial adenomas, reinforced the diagnosis of tuberous sclerosis. A chest tube was placed to treat the pneumothorax, but treatment of the renal angiomyolipomas and lymphangioleiomyomatosis proved more difficult. A decision was made to begin treatment with sirolimus, which has been documented in a recent RCT to be effective in reducing the size of renal angiomyolipomas and improving spirometric measurements in patients with lymphangioleiomyomatosis from tuberous sclerosis.
DISCUSSION: Tuberous sclerosis is a disease of widespread hamartomas, commonly in the CNS, kidneys, and skin, commonly identified clinically with a triad (Vogt's triad) of seizures, mental retardation, and facial angiofibromas. However, these hamartomas can occur in almost any organ system, including pulmonary lymphangioleiomyomatosis, renal angiomyolipomas, cardiac rhabdomyoma, retinal nodular hamartomas, and CNS cortical tubers and supendymal nodules. Enlargement of renal angiomyolipomas pose a significant threat of pain and enlargement with possibility of hemorrhage, and renal cell carcinoma can rarely occur in less that two percent of patients. Trials involving use of sirolimus as a suppressor of mTOR (mammalian target of rapamycin) signaling have found a significant reduction in the size of renal angiomyolipomas during the duration of administration. The major pulmonary manifestation in women with tuberous sclerosis is lymphangioleiomyomatosis, which is characterized by formation of parenchymal cysts and the infiltration of smooth muscle cells. With sirolimus treatment of tuberous sclerosis patients, gas trapping and airflow can improve significantly. However, the most common cause of death is neurologic disease, such as status epilepticus and subependymal giant cell tumors, which are not affected by sirolimus treatment. The manifestations of tuberous sclerosis are numerous and, as in our patient, become more obvious with more complications. It remains crucial for clinicians to identify the constellation of findings in order to diagnose the disease as early as possible, and consider innovative treatments such as sirolimus.

Mystery Case

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Case: A 42 year-old African American man with type II diabetes mellitus presented with pre-syncope and diabetic ketoacidosis.