



EDUCATIONAL OBJECTIVE: Readers will identify potential causes of muscle weakness, including endocrine causes

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Progressive muscle weakness: More there than meets the eye

OUR PATIENT, A 56-YEAR-OLD WOMAN, presents with proximal muscle weakness in all four limbs. It started a few months ago and has gradually become severe, so that she now has difficulty rising from a seated position and has trouble opening jars. She has fallen several times. She says she has no muscle pain, difficulty swallowing, or difficulty breathing.

She sought medical attention at another hospital and was found to be hypothyroid, with a thyrotropin (thyroid-stimulating hormone [TSH]) level of 38 μ U/mL (reference range 0.4–5.5), for which she was started on levothyroxine (Synthroid) 100 μ g daily. She also had a low serum potassium level, for which potassium supplements and spironolactone (Aldactone) were started. She was taking furosemide (Lasix) 20 mg/day at the time.

Despite the thyroid replacement therapy, she continued to become weaker and had more falls. She also noticed a new, nonpainful rash on her lower abdomen.

Review of systems

- Night sweats
- Leg swelling
- Puffiness and discoloration around the eyes, with easy bruisability.

Medical history

- Diabetes mellitus
- Seizures in the 1970s
- Resection of a thymic tumor in 2003 (the exact pathology is unknown)
- Cirrhosis of unknown etiology
- No known history of hypertension

- No history of alcohol or intravenous drug use
- Quit smoking many years ago
- Coronary artery bypass surgery in 2003
- One sibling with myasthenia gravis.

Medications

- Levothyroxine
- Rosuvastatin (Crestor)
- Omeprazole (Prilosec)
- Spironolactone
- Furosemide
- Potassium chloride
- Metoprolol tartrate (Lopressor)
- Metformin (Glucophage)
- Ramipril (Altace).

Physical examination

She is hemodynamically stable and is not hypertensive. Her thyroid is not enlarged. Her lungs are clear to auscultation. Her heart sounds are normal, except for a nonradiating pansystolic murmur most audible at the apex.

Her abdomen is soft and is not distended. Her abdominal rash has a dermatomal distribution consistent with an L1 distribution, with vesicles over an erythematous base. Purpuric lesions are noted over her lower extremities.

Her leg strength is 3 on a scale of 5 on both sides; her arm strength is normal. Ankle and knee reflexes are absent bilaterally.

Initial laboratory analysis

Initial laboratory analysis (TABLE 1) indicates mild renal insufficiency, hypokalemia, elevated liver enzymes, and a normal TSH level. An acetylcholine receptor antibody assay is negative. Her creatine kinase level is also normal.

She has had progressive weakness for several months; what is the cause?

TABLE 1

The patient's general biochemistry values

SUBSTANCE	REFERENCE RANGE	VALUE
Glucose	65–100 mg/dL	154
Sodium	132–148 mmol/L	145
Potassium	3.5–5.0 mmol/L	3.1
Creatinine	0.70–1.40 mg/dL	1.64
Blood urea nitrogen	8–25 mg/dL	77
Chloride	98–110 mmol/L	115
Carbon dioxide	23–32 mmol/L	16
Thyrotropin (TSH)	0.400–5.500 μ U/mL	2.57
Creatine kinase	30–220 U/L	92
Acetylcholine receptor antibody	0.0–0.4 nmol/L	0.0

Up to 10% of patients on statins develop myalgia

PROGRESSIVE MUSCLE WEAKNESS

1 What are possible causes of her muscle weakness?

- ☐ Myasthenia gravis
- ☐ Hypothyroidism
- ☐ Dermatomyositis-polymyositis
- ☐ Drug-induced myopathy
- ☐ Cushing syndrome
- ☐ All of the above

All of these are potential causes of muscle weakness.

Myasthenia gravis

Myasthenia gravis, an autoimmune disease, can affect people of all ages and either sex. It presents with muscle weakness and fatigability, which characteristically fluctuate during the day. Some patients present in crisis with respiratory failure, which may require ventilatory support.^{1,2}

Myasthenia gravis is characterized by autoantibodies against the postsynaptic membrane of the neuromuscular junction. Most patients have antibodies to the extracellular portion of the acetylcholine receptor; a small number of patients have antibodies against a muscle-

specific tyrosine kinase that interacts with this receptor.

About 15% of patients with myasthenia gravis have a thymoma thought to be involved in the pathogenesis of the disease. Treatments include immune suppressive therapy and thymectomy.

Our patient has a history of thymic lesion resection, but her antibody workup for myasthenia gravis was negative.

Hypothyroidism

Hypothyroidism, the most common disorder of the thyroid gland, is especially prevalent in women.³ Its common symptoms include fatigue, exercise intolerance, muscle weakness, cramps, and stiffness.

Both the TSH and the free thyroxine (T_4) level must be measured to diagnose hypothyroidism. This information can also help differentiate primary hypothyroidism (ie, due to a defect in the thyroid gland) from secondary hypothyroidism (ie, due to a defect in the pituitary gland). Elevated TSH with low free T_4 levels indicates primary thyroid failure, whereas the combination of a normal or low TSH and a low free T_4 usually indicates pituitary failure. Subclinical hypothyroidism is characterized by mildly to moderately elevated TSH, but total T_4 and free T_4 values are still within the reference range. Replacement therapy is with levothyroxine.^{3–6}

Our patient has a history of hypothyroidism, which could explain her muscle weakness, but she is currently on replacement therapy, and her TSH level on admission was normal.

Dermatomyositis-polymyositis

Dermatomyositis-polymyositis is characterized by proximal muscle weakness, creatine kinase elevation, erythema on sun-exposed skin, heliotrope rash, and Gottron papules. It occurs mostly in women after the second decade of life. Some medications have been implicated in its pathogenesis, such as statins, fibrates, hydroxyurea, penicillamine, and omeprazole (Prilosec).⁷

In a middle-aged patient, this diagnosis should prompt a search for cancer, especially of the gastrointestinal system, breast, and lung.⁸ Cancer can arise up to 3 years after the

diagnosis of dermatomyositis or polymyositis.

Antisynthetase antibody syndrome is suspected if the patient is positive for antisynthetase antibody and has the following manifestations: acute onset of disease, constitutional symptoms, interstitial lung disease, inflammatory arthritis, mechanic's hands (thickened, cracked skin on the palmar aspect of the thumb and index finger), and Raynaud phenomenon.^{4,8,9}

The diagnosis is made by a thorough clinical evaluation. Electromyography can show an inflammatory pattern of myopathy. The gold standard test for this diagnosis is muscle biopsy.

Our patient has a normal creatine kinase level, which excludes the diagnosis of dermatomyositis-polymyositis.

Statin-induced myopathy

Up to 10% of patients taking statins develop myalgia. Rhabdomyolysis, the extreme form of myopathy, is rare.

The exact mechanism of statin-induced myopathy remains unclear; mitochondrial dysfunction, cholesterol composition of cell membranes, and coenzyme Q10 deficiency have been proposed.

Risk factors for statin-induced myopathy include female sex, older age, higher doses of statins, a family history of statin-induced myopathy, and hypothyroidism. Drugs that increase the risk include fibric acid derivatives, macrolides, and amiodarone (Cordarone). If a statin and any of the above drugs are both required, certain statins—ie, pravastatin (Pravachol) and rosuvastatin—are recommended, since they are the statins least likely to cause rhabdomyolysis.^{5,7,10–12}

The combination of fluvastatin (Lescol) and gemfibrozil (Lopid) has also been found to be safe.¹³ In a crossover study in 17 patients, no significant difference was seen in the area under the curve for plasma concentration over time, in the maximum plasma concentration, or in the time to maximum concentration with the combination vs with each drug alone.¹³

Our patient is taking a statin and has hypothyroidism, which increases the risk of statin-induced myopathy. However, her creatine kinase level is normal.

The cortisol cascade

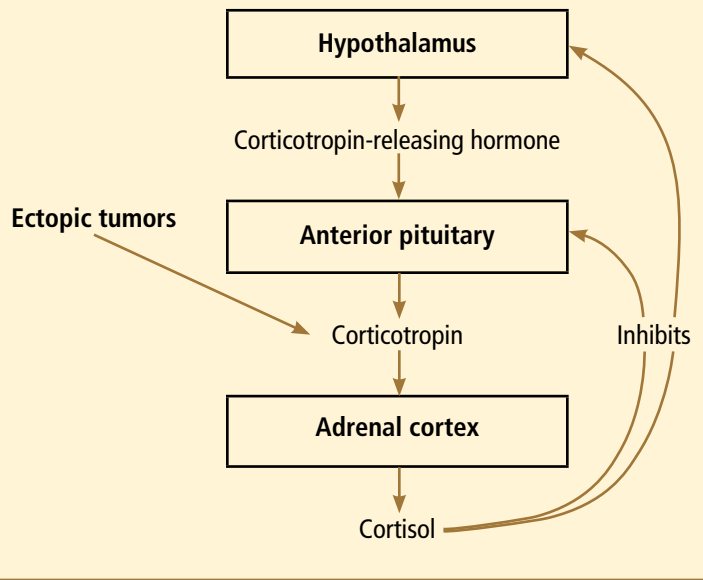


FIGURE 1

Cushing syndrome

Cushing syndrome (hypercortisolism) is one of the most challenging endocrine diseases to diagnose. Most of its clinical features overlap with those of common diseases, and some patients have an atypical clinical presentation with only isolated symptoms. Further, its presentation can be subtle, with weight gain, amenorrhea, muscle weakness, and easy bruisability. Acne, moon facies, plethora, abdominal striae, and purpura are other common signs. It is three to 10 times more common in women than in men.

Cushing syndrome can be classified according to whether or not the excess cortisol secretion depends on corticotropin (formerly called adrenocorticotrophic hormone or ACTH) (FIGURE 1). In corticotropin-dependent cases, the most common cause is pituitary adenoma. (When Cushing syndrome is due to excessive pituitary secretion of corticotropin, which in turn stimulates the adrenal glands to secrete excessive amounts of cortisol, it is called Cushing disease). Other causes of corticotropin-dependent Cushing syndrome are ectopic corticotropin-producing tumors such as carcinoid tumors or medullary thyroid cancers. Corticotropin-independent Cushing syndrome can be caused by adrenal adenomas,

Cushing syndrome is one of the most challenging endocrine diseases to diagnose

TABLE 2

The patient's immunologic laboratory values

TEST	REFERENCE RANGE	VALUE
CD3 cells	958–2388 cells/ μ L	122
CD4 + CD3 cells	533–1674 cells/ μ L	30
Natural killer cells	102–565 cells/ μ L	51
CD4:CD8 ratio	1.1–3.25	0.37

adrenal carcinoma, and bilateral primary micronodular or macronodular adrenocortical hyperplasia.^{14–17}

However, the most common cause of Cushing syndrome is glucocorticoid therapy.

■ BACK TO OUR PATIENT:
HER CONDITION DETERIORATES

Our patient's physical condition deteriorates, she develops respiratory distress, and she is admitted to the medical intensive care unit. Her mental status also deteriorates, and she becomes lethargic and unresponsive.

She is intubated to protect her airway. After this, she develops hypotension that does not respond to fluid resuscitation and that requires vasopressors. Her condition continues to worsen as she develops acute kidney injury and disseminated intravascular coagulation. Her vesicular rash becomes more widespread, involving the entire trunk.

A workup for sepsis is initiated, but her initial blood and urine cultures are negative. Chest radiography does not reveal any infiltrates. No other source of an infection is found.

Varicella zoster is isolated on viral culture of a specimen obtained from the rash, and a polymerase chain reaction test of her blood shows cytomegalovirus DNA (64,092 copies per mL). Immune suppression is suspected, so a CD4 count is ordered (TABLE 2). Serologic tests for human immunodeficiency virus are negative.

What could have caused our patient to have muscle weakness in addition to disseminated zoster with cytomegalovirus viremia?

The diagnosis here is Cushing syndrome.

■ HOW TO TEST FOR CUSHING SYNDROME

2In any practice, you may meet many perimenopausal women who have complaints of weight gain, amenorrhea, and acne. How can you determine if this is Cushing syndrome? What are the screening tests?

- ☐ 24-Hour urinary cortisol excretion
- ☐ A late-night salivary cortisol level
- ☐ A low-dose dexamethasone suppression test
- ☐ All of the above
- ☐ None of the above

Any of the tests listed here can be used to determine whether this is truly Cushing syndrome.

24-Hour urinary cortisol excretion has a reference range of 20 to 100 μ g/24 hours. However, results may be falsely high in patients who are depressed or who abuse alcohol.

The late-night salivary cortisol level is another useful test.^{14,16,18} Patients with Cushing syndrome are found to have high late-night salivary cortisol levels as compared with normal people, indicating the loss of natural circadian rhythm.^{14,16,18}

The low-dose dexamethasone suppression test, as first described by Liddle in 1960,¹⁹ involved giving dexamethasone 0.5 mg by mouth every 6 hours for 48 hours and measuring the serum cortisol level 6 hours after the last dose. In healthy people, this low dose of dexamethasone suppresses the production of corticotropin by the pituitary gland and in turn the production of cortisol, but in patients with Cushing syndrome the cortisol level remains high. An alternative is the overnight 1-mg dexamethasone suppression test—ie, giving 1 mg of dexamethasone at 11:00 PM and measuring the serum cortisol level early the next morning. Failure of the cortisol level to drop to less than 1.8 μ g/dL suggests Cushing syndrome and warrants a complete evaluation for it.

Confirmatory testing is sometimes needed if patients have mild abnormalities in their screening tests. A combination low-dose dexamethasone suppression test and corticotropin-releasing hormone test can be used to differentiate Cushing syndrome from pseudo-Cushing syndrome. This is performed

The most common cause of Cushing syndrome is glucocorticoid therapy

by giving dexamethasone orally 0.5 mg every 6 hours for 48 hours and then giving ovine-sequence corticotropin-releasing hormone 1 µg/kg intravenously 2 hours after the last dose of dexamethasone. The plasma cortisol value 15 minutes after the dose of corticotropin-releasing hormone is greater than 1.4 µg/dL (38 nmol/L) in patients with Cushing syndrome but remains low in patients with pseudo-Cushing syndrome.

Usually, two tests are needed to diagnose Cushing syndrome unless one test is highly abnormal, as seen in our patient, who had an extremely high 24-hour urinary cortisol secretion (TABLE 3).

Is this corticotropin-dependent or corticotropin-independent?

Once Cushing syndrome is diagnosed by one of the screening methods described above, the source of the excess glucocorticoids needs to be determined. Measuring the serum corticotropin level early in the morning would be the next step.

A low corticotropin level (< 10 pg/mL) indicates a corticotropin-independent source, most likely in the adrenal glands. Hence, computed tomography or magnetic resonance imaging (MRI) of the adrenal glands is warranted. Of note: adrenal incidentalomas are quite common, present in 5% of the general population, and a lesion on the adrenal gland does not prove that the patient has primary adrenal disease.^{16,20}

■ IS THE EXCESS CORTICOTROPIN FROM A PITUITARY OR AN ECTOPIC SOURCE?

3 If the corticotropin level is elevated, how can you determine if it is from the pituitary or from an ectopic source?

- ☐ MRI of the pituitary gland
- ☐ High-dose dexamethasone suppression test
- ☐ Corticotropin-releasing hormone stimulation test
- ☐ Bilateral inferior petrosal sinus sampling

If the corticotropin level is high (> 10 pg/mL), it is of paramount importance to determine whether the corticotropin comes from the pituitary gland or from an ectopic source.

TABLE 3

The patient's endocrine laboratory values

TEST	REFERENCE RANGE	VALUE
24-Hour urine cortisol	10–100 µg/day	23,965
5-HIAA random urine creatinine	0.0–9.9 µg/mg	99.8
Corticotropin (ACTH)	8–42 pg/mL	535
Calcitonin	< 8 pg/mL basal ^a < 90 pg/mL peak	213
DHEA-S	10–152 µg/dL	195.5

^aIn women

5-HIAA=5-hydroxyindoleacetic acid (a breakdown product of serotonin);

DHEA-S=dehydroepiandrosterone sulfate

MRI of the pituitary gland should be done in patients with suspected corticotropin-dependent Cushing syndrome. However, MRI may be negative in 50% of patients with Cushing disease, and it should therefore not be used for screening. In addition, 10% of the population may have pituitary incidentalomas on MRI.

Most cases of corticotropin-dependent Cushing syndrome are caused by microadenomas (smaller than 1 cm), while a few cases are caused by macroadenomas (larger than 1 cm). If a microadenoma is found on MRI, further testing with bilateral inferior petrosal sinus sampling is recommended (described below); if a macroadenoma is found, then no further testing is required.^{21,22} In fact, patients who have biochemical findings compatible with Cushing disease (ie, due to an overactive pituitary) and who have an adenoma larger than 6 mm do not require further evaluation.²³

A high-dose dexamethasone suppression test involves giving 8 mg of dexamethasone in the evening and measuring the cortisol level the next morning. If the cortisol level declines to 50% of the baseline level after this dose, this suggests a pituitary cause.

Corticotropin-releasing hormone stimulation testing. In most cases of pituitary tumors and a few cases of ectopic corticotropin-secreting tumors, giving corticotropin-releasing hormone leads to an increase in serum corti-

If corticotropin is > 10 pg/mL, find out whether it comes from the pituitary or from an ectopic source

The patient was too ill to undergo additional imaging

cortropin and cortisol levels. In contrast, these levels do not respond to corticotropin-releasing hormone stimulation if the problem is in the adrenal gland. The test is performed by giving 1 µg/kg or 100 µg synthetic or human corticotropin-releasing hormone. A 35% to 50% increase above baseline in corticotropin suggests a pituitary cause.²³

Bilateral inferior petrosal sinus sampling can be used to confirm a pituitary source, as it is the gold standard for differentiating ectopic from pituitary corticotropin production. Once this is confirmed, a neurosurgical consult is warranted.^{16,18}

This procedure is usually done by advancing a sheath from the femoral vein to reach the inferior petrosal sinuses. Blood samples are obtained from both the inferior petrosal sinuses and from a peripheral vein to measure corticotropin levels before and after giving corticotropin-releasing hormone (1 µg/kg). Before corticotropin-releasing hormone is given, a gradient of central-peripheral corticotropin levels of 2.0 or greater indicates a pituitary source. With ectopic corticotropin production, the corticotropin gradient is usually less than 1.5. Corticotropin-releasing hormone is given to increase the sensitivity: after it is given, a gradient of 3.0 or greater is considered indicative of Cushing disease.²⁴

If the corticotropin level is elevated and the above tests indicate ectopic production, the source should be sought. The most common site of ectopic corticotropin production is the chest. Common causes are bronchial, thymic, and pancreatic carcinoid tumors. Other causes are small-cell lung cancer, medullary cell cancer, and pheochromocytoma.^{15,18,25}

■ BACK TO OUR PATIENT

Our patient's further laboratory results are listed in **TABLE 3**.

She has elevated 24-hour urinary cortisol excretion, consistent with Cushing syndrome. Her corticotropin level is elevated, which rules out an adrenal cause. Her 5-HIAA (a serotonin breakdown product) and calcitonin levels are also elevated, suggesting either medullary thyroid cancer or a carcinoid tumor. She also has a mild elevation of dehydroepiandrosterone sulfate, which is consistent with

corticotropin-dependent Cushing syndrome.

Our patient's elevated levels of cortisol were the cause of her muscle weakness and severe immune deficiency, which in turn led to cytomegalovirus viremia and sepsis. Cushing syndrome usually causes hypertension, especially in cases of ectopic corticotropin production. However, our patient was normotensive on admission and then developed cytomegalovirus sepsis, which led to hypotension and shock.

Immune suppression is a well-known effect of glucocorticoids.^{26–28} Kronfol et al²⁸ found that CD4 and CD8 counts and the CD4-to-CD8 ratio were low in patients with Cushing syndrome, and natural killer cell activity was suppressed. Opportunistic infections have been described in patients with Cushing syndrome.^{26,27,29}

■ MANAGEMENT OF CUSHING SYNDROME

Management of Cushing syndrome should be tailored after determining its source.

A neurosurgical consultation is warranted in cases of pituitary adenoma, with surgical resection of the adrenal source or ectopic tumor if feasible.²⁵

Medical management is recommended if surgical resection is not possible.^{30,31} Several drugs can be used to inhibit cortisol synthesis in this situation.^{30,32}

Adrenal-acting agents

Aminoglutethimide (Cytadren) acts by blocking the conversion of cholesterol to pregnenolone, a precursor of cortisol. The dosage is 250 mg twice or three times a day. This drug is no longer available in the United States.

Ketoconazole (Nizoral) inhibits side-chain cleavage, 11-beta hydroxylase, and 17-alpha hydroxylase, thus inhibiting cortisol synthesis; it also inhibits corticotropin secretion. The dosage is 200 to 400 mg three times a day.

Metypapone (Metopirone) blocks 11-beta-hydroxylation of deoxycortisol, the reaction that produces cortisol. The dosage is 500 to 750 mg three times a day. This drug can be obtained only from the manufacturer and only on a named-patient basis.

Etomidate (Amidate), an anesthetic drug,

also blocks 11-beta-hydroxylation of deoxycortisol. It is given intravenously at a rate of 0.3 mg/kg per hour.

Centrally acting agents

Cabergoline (Dostinex). It is believed that corticotropin-producing pituitary tumors express D2 receptors. Cabergoline is a dopamine agonist that has been used in patients with Cushing disease. The dosage is 0.5 to 7 mg/week.

Pasireotide is still investigational. It is a somatostatin receptor agonist given subcutaneously for 15 consecutive days to patients with Cushing disease.

Glucocorticoid receptor antagonist

Mifepristone (Mifeprex) is a progesterone receptor and glucocorticoid II receptor

antagonist that is being investigated in the treatment of persistent or recurrent Cushing disease. It is not yet approved by the US Food and Drug Administration for this indication.

■ BACK TO OUR PATIENT

The patient was too ill to undergo additional imaging, including octreotide scanning to identify an ectopic corticotropin-secreting tumor. She was medically treated with intravenous etomidate to reduce her cortisol level.^{30,31}

Unfortunately, our patient died of multiorgan failure. The exact site of her ectopic corticotropin-producing tumor was never identified, and no autopsy was done. ■

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