Leg Discomfort: Beyond the Joints

Douglas Berger, MD, MLitt

KEYWORDS

• Leg pain • Paresthesia • Claudication • Neuropathy • Myalgia • Cramp

KEY POINTS

- Although simple characterization of discomfort as cramps, heaviness, shooting pains, and so forth can be misleading, history and examination are key to accurate diagnosis.
- Absence of both dorsalis pedis and posterior tibial pulses strongly suggests peripheral arterial disease (PAD), and the presence of either pulse makes PAD less likely.
- Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are a common cause of lower extremity myalgias.
- Restless legs syndrome causes nocturnal discomfort but must be distinguished from confounding "mimics."
- Neurologic causes of leg symptoms include lumbar spinal stenosis, radiculopathy, distal symmetric polyneuropathy, and entrapment neuropathy.
- Many common causes of leg discomfort can be managed conservatively.

INTRODUCTION

Discussions of leg pain usually begin with the hip, knee, and ankle. For each joint there are well-established differential diagnoses and physical examination maneuvers. Nonetheless, patients often present with discomfort that after brief history taking and examination seems unrelated to the joints and periarticular structures. Such symptoms are challenging for primary care providers because the range of possible causes is large, ill defined, and runs from benign cramps to life-threatening deep vein thrombosis (DVT). Moreover, leg symptoms can be difficult for patients to describe, and terms such as cramps or heaviness can lead clinicians to an overly narrow set of diagnostic considerations.

Leg discomfort is common, occurring in two-thirds of elderly Iowans[1] and outpatient veterans.[2] However, symptoms do not correlate well with disease. Carefully designed studies assessing the prevalence of lower extremity arterial[3] and venous[4] disease found background rates of exertional symptoms and "tired/heavy legs" as high as 40% to 60% with relatively small differences between those with and without evidence of vascular disease. Use of a survey designed to distinguish between cramps, restless

General Medicine Service, Department of Medicine, VA Puget Sound, University of Washington, 1660 South Columbian Way, Seattle, WA 98108, USA
E-mail address: douglas.berger@va.gov

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legs syndrome (RLS), and peripheral neuropathy resulted in 20% of patients classified as having all 3 diagnoses.[2] Thus, simple symptom checklists are unlikely to yield an accurate diagnosis of leg symptoms.

Causes of leg discomfort are too numerous to list. Rather, this article presents common causes of leg pain, paresthesias, cramping, heaviness, and numbness arising outside the joints. The discussion is organized into vascular, neurologic, and musculoskeletal sources of pain; it is often helpful to consider each of these 3 categories when evaluating patients with leg discomfort.

VASCULAR CAUSES OF LEG DISCOMFORT

Lower Extremity Peripheral Arterial Disease

Atherosclerosis of arteries supplying the legs occurs in 3% to 10% of adults and up to 15% to 20% of those older than 70 years.[5] Risk factors are similar to those for coronary artery disease.

The classic symptom of peripheral arterial disease (PAD) is intermittent claudication: muscle fatigue, aching, cramping, numbness, or heaviness that comes with exertion and is relieved by rest within 10 minutes.[5] Severe PAD can cause critical limb ischemia: ulceration, gangrene, or constant pain when at rest that is worse with elevation and improved with dependency. Although claudication most commonly affects the calves, other areas may be affected depending on the location of stenosis:

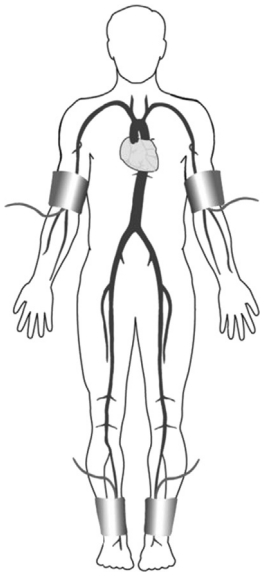
- Aortoiliac occlusion: buttock and hip claudication, erectile dysfunction in men
- Iliofemoral occlusion: thigh claudication
- Femoral or popliteal occlusion: calf claudication
- Tibial or peroneal occlusion: foot claudication[6]

Only 20% of patients with PAD endorse classic claudication symptoms. Some are asymptomatic; many have atypical exertional symptoms.[3,7] Although a history of claudication increases the likelihood of PAD (likelihood ratio [LR] 3.3), the absence of classic claudication does not rule out even moderate to severe PAD (LR 0.57).[8] Physical examination is more helpful. Absence of both dorsalis pedis and posterior tibial pulses strongly suggests PAD (LR 14.9), and the presence of either pulse makes PAD less likely (LR 0.3).[9] A significant subset of healthy adults will lack one pulse, but usually the other vessel compensates, leaving only 1% to 2% of healthy adults lacking both pulses.[9] The presence of an iliac, femoral, or popliteal bruit is also suggestive of PAD (LR 5.9 for symptomatic patients), and absence of all 3 bruits reduces the likelihood of PAD (LR 0.38).[8,9] Wounds, skin discoloration, and temperature asymmetry increase the probability of PAD in symptomatic patients, but absence of these features is not helpful.[8,9] Bruits and pulses may also help clinicians locate the level of stenosis.[9]

Guidelines recommend that all patients with exertional leg symptoms be evaluated with an ankle-brachial index (ABI).[5,10] This noninvasive test (**Table 1**) has become standard for diagnosis and correlates exceptionally well with angiography (95% sensitivity and nearly 100% specificity).[5,10,11] Symptomatic patients with a normal or noncompressible ABI should be further investigated, usually with ABI after exertion or a toe-brachial index, respectively. Other tests may be used to diagnose PAD and identify the level of occlusion, but arterial imaging is usually reserved for preprocedural planning or investigating nonatherosclerotic causes of PAD.[10]

Symptomatic PAD without critical limb ischemia has a favorable prognosis in the leg: only 10% to 20% have progressive symptoms and only 1% to 2% develop critical limb ischemia over 5 years.[10] However, cardiovascular morbidity is high, with a 4% to

Table 1
Ankle-brachial index (ABI)



Preparation: Patient lies supine for 10 min in a warm room
Measurement: Systolic pressures are measured at the brachial, dorsalis pedis (DP), and posterior tibial (PT) arteries bilaterally, usually using a handheld Doppler probe and appropriately sized sphygmomanometer cuffs
Calculation:
Right ABI:
Higher of the right ankle pressures (DP or PT)
Higher of the brachial pressures (left or right)
Left ABI:
Higher of the left ankle pressures (DP or PT)
Higher of the brachial pressures (left or right)
Interpretation: (revised 2011)[11]
- ≤0.9: Peripheral arterial disease
- 0.91–0.99: Borderline
- 1–1.4: Normal
- >1.4: Noncompressible arteries

Variations:
- Exercise ABI: Repeat measurement after exercise (treadmill, stairs, pedal plantar flexion). Decrease in ABI of 15%–20% is considered diagnostic of PAD[5]
- Toe-brachial Index: Used in cases of noncompressible arteries (ABI>1.4); this procedure requires special equipment

Adapted from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5–67; with permission.

7% risk of nonfatal myocardial infarction or cardiovascular death annually.[5] Therefore, treatment is focused on reducing cardiovascular risk with aspirin or clopidogrel, statins, management of hypertension, and smoking cessation. For the leg, exercise, medications (eg, cilostazol), and revascularization reduce symptoms.[5,10] Data from an ongoing randomized trial suggest that for aortoiliac PAD, supervised exercise may yield larger gains in walking distance than endovascular intervention.[12] New evidence also suggests benefit from unsupervised home exercise.[13]

Chronic Venous Disease

Just as inadequate arterial supply to the legs can cause discomfort, so too can problems with venous return. Chronic venous insufficiency may be due to primary weakness of vein valves or walls. Secondary causes include prior DVT (postthrombotic syndrome) or other mechanical obstruction, such as occlusion of the left iliac vein by the right iliac artery (May-Thurner syndrome). Beyond a history of thrombosis or thrombophilia, risk factors include family history, female sex, age, obesity, greater height, prolonged standing, and multiple pregnancies.[14]

Venous disease is said to cause leg tingling, aching, burning, pain, cramps, throbbing, heaviness, pruritus, restlessness, and fatigue.[15] Empirically, aching, heaviness, and pruritus correlate best with ultrasonographic findings.[4,16,17] Symptoms are usually worse with dependency and improve with walking or elevation,[18] which facilitate venous return. Obstruction of deep veins rarely causes symptoms that worsen with activity, leading to the term “venous claudication”.[5]

Most patients with discomfort attributable to venous disease will have visible vascular abnormalities or associated skin changes (**Fig. 1**).[18] Duplex ultrasonography is the preferred test to confirm the diagnosis as well as to identify and localize

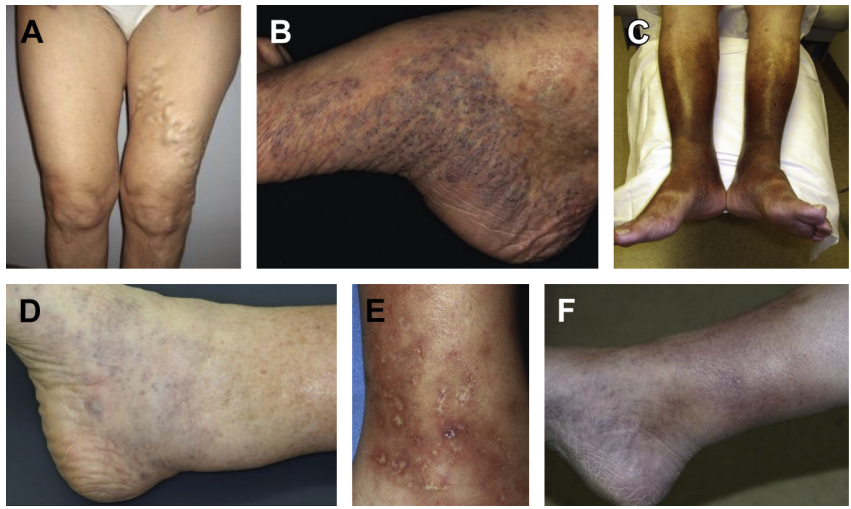


Fig. 1. Common skin changes associated with venous insufficiency. (*A*) Large varicose veins. (*B*) Venulectasias of the instep, sometimes called corona phlebectatica or ankle flare. (*C*) Hemosiderin deposition in the "gaiter area." (*D*) Edema localized to the ankle. Note also reticular veins in the instep and hemosiderin deposition above the ankle. (*E*) Atrophie blanche. (*F*) Lipodermatosclerosis. ([*A*] *From* Stoughton J. Venous ablation therapy: indications and outcomes. Prog Cardiovasc Dis 2011;54(1):63; with permission; [*B, E, F*] *From* Hafner A, Sprecher E. Ulcers. In: Bolognia JL, Jorizzo JL, Schaffer JV, et al, editors. Dermatology. 3rd edition. St. Louis, Mo: Saunders; 2012. p. 1729–46; [*C*] *From* Beckman JA, Creager MA. The history and physical examination. In: Vascular medicine: a companion to Braunwald's heart disease. 2nd edition. Philadelphia: W.B. Saunders; 2013. p. 139–47; with permission; and [*D*] *From* Hoffbrand AV, Pettit JE, Vyas P. Color atlas of clinical hematology. Philadelphia: Mosby/Elsevier; 2010. p. 474; with permission.)

underlying reflux or obstruction. Plethysmography and other tests may be used as adjuncts.[15]

Conservative treatments include compression (**Box 1**), weight loss, exercise, and elevation of the legs above the level of the heart.[18–21] Medical therapy is limited. Diuretics make little sense in the absence of systemic volume overload. Pentoxifylline provides limited benefit in venous ulceration but is not widely used.[18] Among several herbal preparations, horse chestnut seed extract (escin) has been shown to reduce symptoms and edema in short-term trials.[22] Surgical/interventional treatments include venous destruction with chemical sclerosants or thermocoagulation, ablation with radiofrequency or laser, stripping, or excision. In agreement with guidelines from surgical/interventional societies,[15,23] recent guidelines from the British National Institute for Health and Care Excellence[24] recommend ultrasonographic evaluation for patients with symptomatic varices, and interventional or surgical treatment rather than compression alone for symptomatic patients with truncal reflux.

Acute Deep Vein Thrombosis

Leg DVT is often asymptomatic but can cause pain, swelling, redness, and warmth. Risk factors can be as important diagnostically as symptoms or signs. Diagnosis usually relies on a combination of structured risk-stratification tools and noninvasive testing including serum D-dimer and ultrasonography. The most studied risk-stratification tool is the Wells score (**Table 2**).[25,26] In general, for patients with a low pretest probability

Box 1
Compression therapy for venous disease

Indications and Limitations for Use:

- Strong evidence for improved healing of venous ulcers[19] with limited evidence of symptomatic benefit in less severe disease.[20]
- Compression is contraindicated in patients with severe PAD for fear of decreasing arterial perfusion.[18]
- Risks include contact dermatitis and decreased venous return from bunching of poorly fit stockings.[20]
- Discomfort and difficulty donning stockings markedly limit adherence.[18]

Tips for Use of Compression Therapy in Chronic Venous Disease:

- Graduated compression (higher pressure distally) is preferred over fixed compression.[18] Multicomponent stockings with elastic may be more effective than single-component stockings.[19]
- Even in patients with proximal obstruction, compression is most important below the knee. Choice of height (knee, thigh, or waist) should be based on patient preference.[21]
- For edema caused by chronic venous disease, 20 to 30 mmHg pressure at the ankle typically suffices. Patients with venous dermatitis or ulcer may benefit from 30 to 40 mmHg if tolerable. Over-the-counter and antiembolic stockings used for DVT prophylaxis provide only 10 to 20 mmHg of pressure.
- Several varieties of stocking donners are available. Use of powder or liner hose may also help.
- Custom stockings are available if off-the-shelf stockings do not fit.

based on the Wells or similar validated score, a negative D-dimer is sufficient to rule out DVT without ultrasonography.[27] In higher-risk populations, depending on the details of the laboratory method, D-dimer may or may not be diagnostically helpful, and patients often need imaging.[27]

Table 2
Wells score for deep vein thrombosis

Clinical Feature	Score
Active cancer (treatment ongoing or within previous 6 mo or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 d or more, or major surgery within 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	−2
Risk scoring: low ≤0, moderate 1–2, high ≥3	

A revised Wells score[26] includes prior deep vein thrombosis as an additional risk factor, lengthened the postoperative risk period, and made several smaller textual changes. A revised score of <2 is considered low risk.

Adapted from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997;350(9094):1795–8; with permission.

Although anticoagulation is the primary therapy for proximal DVT, in symptomatic patients compression therapy is an important adjunct. Initiating compression within 2 weeks and continuing for 2 years can reduce the incidence of postthrombotic syndrome by 50%.[27]

Other Vascular Causes of Leg Pain

Rare nonatherosclerotic causes of arterial obstruction include arterial dissection, aneurysm, embolism, arteritis, trauma, and external compression.[5] In the leg, arterial endofibrosis and popliteal artery entrapment may occur in athletes.[28]

NEUROLOGIC CAUSES OF LEG DISCOMFORT

Lumbosacral Radiculopathy and Lumbar Spinal Stenosis

Lumbosacral radiculopathy and lumbar spinal stenosis (LSS) often cause low back pain, but may present primarily or exclusively with leg symptoms.[29,30] Radiculopathy is most commonly caused by nerve-root compression from a herniated intervertebral disc. Bony disease, malignancy, epidural abscess, and even noncompressive etiologies such as herpes zoster also occur.[31] LSS is characterized by anatomic impingement of the spinal canal, recesses, or foramina owing to degenerative changes of the vertebrae or ligamentous hypertrophy.[30] Radiculopathy frequently presents in middle age.[32] LSS usually affects the elderly.[33]

Radiculopathy is defined by radiating pain, paresthesias, or other sensory changes in a dermatomal distribution, sometimes with weakness or reflex changes in the corresponding myotome (**Table 3**).[29] However, there are conceptual limits to dermatomal and myotomal mapping[34] and empirically, pain may not follow the classic dermatomes.[35,36] Other features, such as worsening with Valsalva, have not been validated. A host of examination maneuvers designed to stretch the nerve roots[34] are of limited value. The straight-leg raising (SLR, Lasègue) test, consisting of reproduction of radiating pain by passively elevating the affected leg of a supine patient, contributes little when positive (LR 1.5), but may argue against compressive radiculopathy when

Table 3
Lumbosacral radiculopathies causing leg discomfort

Root Level	Dermatome	Myotome	Reflex Affected	Selected Mimics[a]
L2	Anterolateral thigh	Hip flexion		Lateral femoral cutaneous neuropathy
L3	Medial thigh and knee	Hip flexion and adduction, knee extension	Knee jerk	
L4	Medial lower leg	Knee extension and hip adduction	Knee jerk	
L5	Lateral lower leg, dorsum of foot, great toe	Ankle dorsiflexion, foot inversion/eversion and toe flexion/extension		Peroneal neuropathy
S1	Lateral foot and toes, sole	Foot plantarflexion, knee flexion, hip extension	Ankle jerk	Sciatic neuropathy

Underlined findings have empirical support as useful in identifying the level of radiculopathy.
[a] All can be mimicked by spinal stenosis or lumbosacral plexopathy.
Data from Refs.[9,29,31]

absent (LR 0.4).[9] Pain on raising the unaffected leg (crossed SLR) suggests radiculopathy (LR 3.4), as do calf wasting and weak ankle dorsiflexion.[9,37]

Although LSS can also cause radiculopathy symptoms, it typically causes neurogenic claudication: a feeling of pain, weakness, or fatigue in the buttocks or legs provoked by walking and relieved by rest.[30] Patients may also describe numbness and tingling. Unlike radiculopathy, the symptoms are often bilateral.[38] Isolating leg exertion from spinal flexion can help distinguish arterial from neurogenic claudication (**Table 4**). Using expert opinion as the reference standard, bilateral buttock or leg pain, relief with sitting or bending, and rare urinary/anogenital symptoms increase the likelihood of spinal stenosis (LR>5). Absence of these key historical features decreases the likelihood of LSS (LR near 0.3):

- Age older than 65
- Neurogenic claudication
- Pain below the buttocks
- Pain in the thigh
- Aggravation by standing/walking and relief by sitting

On examination, wide-based gait and abnormal Romberg test are most helpful in identifying LSS (LR>4), with strength, sensory, and reflex abnormalities less helpful (LR 2–3).[39,40]

Magnetic resonance imaging is the diagnostic test of choice for LSS[30,40] and also when imaging is required for suspected radiculopathy.[41] Specificity is low; 20% to 30% of adults have imaging consistent with disc herniation,[32] and an equal proportion older than 55 years have radiographic evidence of LSS.[39] Electrodiagnostics can demonstrate and localize radiculopathy but may be normal in sensory-only radiculopathy.[29] The role for electrodiagnostics in diagnosis of LSS remains controversial.[30,42]

The prognosis of acute lumbosacral radiculopathy is good, with pain and weakness often resolving over days to weeks and more than two-thirds of patients recovering within a year.[41] Acute management is usually conservative and imaging unnecessary, unless there is abnormal perineal sensation, sexual, bladder, or bowel control suggestive of cauda equina syndrome; rapidly progressive neurologic deficits; or risk for epidural abscess or malignancy.[31,41] Similarly, the natural history of untreated spinal stenosis is favorable for many patients.[30] In a small study, over 4 years two-thirds of patients had no change in pain, with the remainder split between improvement and worsening.[43]

There is little evidence of benefit from conservative treatments for either condition including medications, physical therapy, traction, and transcutaneous electrical nerve stimulation (TENS).[30,41,44,45] Use of epidural steroid injections is controversial, with

Table 4
Conceptual distinction between vascular and neurogenic claudication

Vascular Claudication	Neurogenic Claudication
Triggered by increased demand across arterial stenosis. Relieved by rest	Triggered by lumbar extension worsening spinal stenosis. Relieved by lumbar flexion
Pain reliably comes after a fixed amount of exertion (eg, specific walking distance)	Pain may come with minimal exertion (eg, standing in line, going down stairs)
Pain comes with activity even if back is flexed (eg, riding a bicycle)	Pain does not occur with exertion in lumbar flexion (eg, leaning on a shopping cart)

statistically but perhaps not clinically significant benefit.[30,41,46] Surgery for radiculopathy and LSS likely yields at least short-term symptomatic benefit; analysis of randomized trials has been limited by crossover between surgical and nonsurgical arms.[47,48]

Entrapment Neuropathies

Most entrapment neuropathies of the leg are rare outside of surgical settings, or present primarily with weakness rather than pain or paresthesias.[49] Primary care providers will often encounter lateral femoral cutaneous neuropathy (LFCN, also called meralgia paresthetica from the Greek for "thigh pain"). LFCN is characterized by a sharply demarcated area of numbness and paresthesias on the anterolateral thigh. It is usually caused by compression of this sensory-only nerve as it travels under the inguinal ligament.[49] Obesity, diabetes, and older age are risk factors.[50] Mechanical causes include pregnancy, tight clothing, and heavy tool belts.[49] Diagnostic testing is rarely required, but imaging can be used to rule out rare intra-abdominal abnormality causing compression proximal to the inguinal ligament.[51,52] Reassurance, avoidance of tight clothing and belts, and weight loss are the mainstays of treatment. Neuropathic and other pain medications may be used. Local injections and surgery are rarely required.[53]

Peroneal neuropathy is the most common compression neuropathy of the leg.[49] It is characterized primarily by foot-drop and falls, although there may be pain changes over the lateral calf and dorsum of the foot. Peroneal neuropathy is typically caused by compression or entrapment at the fibular neck caused by leg crossing, squatting, or weight loss. Piriformis syndrome is a controversial diagnosis whereby the sciatic nerve is said to be compressed by the piriformis muscle at the sciatic notch.[52]

Distal Symmetric Polyneuropathy

Distal symmetric polyneuropathies (DSP) have a distribution that is length dependent rather than following a single nerve or dermatome.[54] Symptoms begin in the toes and progress proximally up the leg, eventually involving the hands (stocking-glove distribution) and anterior thorax.[55] Of the many metabolic, toxic, endocrine, inflammatory, genetic, and neoplastic causes, diabetes and alcohol misuse are the most commonly seen in primary care.[55,56] DSP affect 30% to 50% of diabetics, although only half are noticed by the patient.[57]

Patients may complain of neuropathic pain, numbness, or a tight, wooden leg, often worse at night or with standing.[58] Examination findings include decreased pain, touch, temperature, vibration, and proprioceptive sensation. In the leg, weakness usually begins in dorsiflexors before plantarflexors.[54] Atrophy may be visible directly or as muscular imbalance leading to hammertoes. Patients may lose the ability to walk on heels before tip-toe.[55] Ankle-jerk reflex may be diminished or absent, although this finding is common among elderly patients without DSP.[54] For diabetics, use of either a tuning fork to test vibratory sensation or a Semmes-Weinstein monofilament can accurately predict neuropathy on nerve conduction study; inability to walk on heels and abnormalities of deep tendon reflexes are less useful.[59]

Electrodiagnostics can confirm the presence of DSP and distinguish between axonal and demyelinating disase.[55,58] Basic laboratory tests include serum glucose/hemoglobin A_{1C}, vitamin B_{12}, serum protein electrophoresis, antinuclear antibody, erythrocyte sedimentation rate, and rapid plasma reagin, with tests for other infectious, autoimmune, toxic, and nutritional causes reserved for select patients or when the initial studies are unrevealing.[55,56] In diabetics with classic symptoms, testing may not be required.[58,60]

There is increasing recognition of DSP involving only the small fibers that transmit pain and touch, leaving other senses, strength, reflexes, and electrodiagnostics unaffected.[54] Such small-fiber neuropathy may be idiopathic in the elderly[58] but is also a cause of atypical diabetic neuropathy occurring in patients without microvascular complications, or even in patients with elevated glucose not meeting criteria for diabetes.[61]

Treatment of DSP is directed at the underlying cause. Multispecialty guidelines also support the use of pregabalin, gabapentin, sodium valproate, venlafaxine, duloxetine, amitriptyline, opioids, capsaicin, isosorbide spray, and percutaneous nerve stimulation.[62]

Other Neurogenic Causes of Leg Discomfort

Numerous neurologic conditions including amyotrophic lateral sclerosis, cervical myelopathy, and Guillain-Barré syndrome cause weakness, gait abnormalities, or sensory changes in the leg.[63] Plexopathies are less common in the leg than in the arm but can be caused by compression, trauma, radiation, and infection.[64] Lumbosacral radiculoplexopathy is a rare syndrome of disabling leg pain and weakness occurring primarily in patients with uncomplicated diabetes.[65]

MUSCULOSKELETAL CAUSES OF DISCOMFORT

Most musculoskeletal leg discomfort derives from the joints or periarticular structures (eg, arthritis, tendinopathy, bursitis) and is not discussed here. It is noteworthy that joint pain may radiate away from the joint; distal radiation of pain from hip arthritis is particularly common.

Stress Fracture

Diagnosis of fracture is clear in the setting of trauma and local tenderness, but pathologic and insufficiency fractures from malignancy and osteoporosis may occur with minimal trauma and cause more diffuse pain. Stress fractures occurring, for example, in the setting of increased athletic training also require a high index of suspicion. Not only can the onset of pain be insidious, but initial radiographs may be normal, necessitating repeat films or advanced imaging. For medial tibia stress fractures, rest, perhaps with immobilization or non–weight bearing, is the primary treatment, although fractures of the anterior cortex may require surgical management.[66]

Statin Myalgia

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) cause myalgia (muscle pain) with or without myopathy (muscle damage) in 5% to 10% of users.[67,68] Myalgia may occur in any part of the body but the legs are most commonly affected, usually the calves and thighs.[69,70] The pain is described as heaviness, stiffness, cramping, and sometimes weakness. It is often exertional, causing patients to limit physical activity. Symptoms start on average 1 month after statin initiation, but can be delayed for 6 to 12 months[69] and can last 2 months after cessation of the medication.[67] Risk of myalgias and myopathy are increased by drug interactions including fibrates and cytochrome P450 3A4 (CYP 3A4) inhibitors (eg, amiodarone, cyclosporine, protease inhibitors, macrolide antibiotics, and calcium-channel blockers). Pravastatin, fluvastatin, and rosuvastatin are less prone to the CYP 3A4 interactions.[67] Low levels of grapefruit consumption are unlikely to be problematic.[71]

Workup of statin myalgias usually includes measurement of serum creatinine kinase (CK) and thyroid stimulating hormone, as thyroid abnormalities can cause hyperlipidemia and myalgia.[68] Statin myalgias in the absence of CK elevations are not

dangerous and need not prompt management changes if they are not of significant concern. Large elevations of CK (>5–10 times the upper limit of normal) may require modification or cessation of statin therapy independent of myalgias.[67] Strategies to address statin myalgia include:

- Cessation of the statin or interacting drugs
- Dose reduction
- Use of an alternative statin (eg, pravastatin, fluvastatin, or rosuvastatin)
- Alternate-day dosing
- Addition of coenzyme Q (limited evidence)[67,68]

Cramps

Cramps are sudden, involuntary, painful, electrically active contractions of skeletal muscle.[72] Leg cramps usually occur in the posterior calf but may involve the foot or the thigh. Cramps often occur at night and last seconds to minutes but may result in prolonged soreness. During the cramp, muscle contraction is usually visible or palpable.[63]

There are long lists of medical conditions said to cause cramps, including pregnancy, dialysis, hypothyroidism, hypovolemic hyponatremia, cirrhosis, radiculopathies, and peripheral neuropathies.[63,73] Many of the associations are based on surveys and must be interpreted cautiously, especially in light of a reported cramp prevalence of 30% to 95% in the general population.[63] One study looking at Canadian pharmacy data suggests a strong association with inhaled long-acting β2-agonists and potassium-sparing and thiazide diuretics, with a weaker association for statins and loop diuretics.[74] Alcohol and calcium-channel blockers are also frequently cited.[63,75–77]

Cramps are diagnosed by history taking, with physical examination and diagnostic testing used to exclude other conditions. Routine evaluation of thyroid function and electrolytes remains controversial, based in part on data suggesting that electrolyte abnormalities do not predict cramps among endurance athletes.[63,75,77] Stretching or massage of the affected muscle can bring acute relief. There is new evidence for prophylactic stretching,[78] which has long been advocated based on anecdotal evidence.[79] As nocturnal cramps have been attributed to shortening of the calf and plantar foot muscles by pressure from bedclothes,[63,76] one might also suggest a blanket lift or other strategy to reduce this pressure. A review by the American Academy of Neurology (AAN) found no evidence for hydration in the prevention of cramps.[72] Quinine, once the mainstay of the pharmacologic treatment of cramps, has modest benefit usually outweighed by the risk of thrombocytopenia, hypersensitivity, and QT prolongation. In 2006 the Food and Drug Administration added a black-box warning advising against off-label use of quinine for cramps, and the AAN review argues that quinine should be avoided for routine treatment and considered only for disabling cramps after specific discussion and informed consent.[72] There is no evidence regarding use of tonic water for cramping. Small studies have suggested that vitamin B_6 (even in nondeficient patients), diltiazem, and natridrofuryl (a vasodilator not approved in the United States) may be helpful.[72] A Cochrane review concluded that magnesium is not helpful in nonpregnant adults.[80]

RESTLESS LEGS SYNDROME

RLS (also called Willis-Ekbom disease) is defined by discomfort and an urge to move the legs that occurs at rest, is relieved by movement, and occurs primarily in the evening or at night. It is often associated with periodic limb movements of sleep. Patients

describe the discomfort as creepy-crawly, jittery, throbbing, tight, tearing, and electric current. RLS affects 1% to 3% of the population and is often familial. An association with age has been shown in some but not all studies. It is associated with iron deficiency, end-stage renal disease, and medications including antidopaminergic neuroleptics and antiemetics, antihistamines, and antidepressants (selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors, but not bupropion).[81]

Although RLS is defined by symptoms, patients with various "mimics" (including cramps, arthritis, and peripheral neuropathies) may meet the original diagnostic criteria.[82] RLS must be distinguished from positional discomfort (eg, crossed legs) and unintentional movements such as hypnic jerks or unconscious foot tapping. Patients with RLS have symptoms in various rest positions and consciously move the leg to relieve symptoms.[82]

Multiple groups have reviewed treatment of RLS,[83–86] including a federally funded analysis[87] free from industry-related conflict of interest. Nonpharmacologic treatments are often favored for mild to moderate disease, with some evidence to support exercise and cognitive-behavioral therapy.[84,87] Mental-alerting activities (eg, crosswords or video games) and avoidance of caffeine are suggested based on expert opinion.[85] It is reasonable to assess iron stores and replete patients with low iron stores. There is less consensus on iron supplementation in patients with low to normal iron levels.[83–86] Dopaminergic medications (eg, pramipexole, ropinirole, rotigotine) are effective but limited by augmentation, the iatrogenic development of more severe symptoms or spread to other limbs earlier in the day, as well as concerns about impulse-control problems. $\alpha 2\delta$ ligands (gabapentin, gabapentin encarbil, and pregabalin) are increasingly considered as first-line agents. Opioids, benzodiazepines, and their respective agonists are used without high-quality supporting evidence.[83–87]

Other Musculoskeletal Causes of Leg Discomfort

Diffuse myalgia may be caused by medications other than statins and a host of infectious, endocrine, metabolic, and rheumatologic diseases.[63] Polymyalgia rheumatica perhaps deserves special mention as a cause of bilateral proximal leg pain and stiffness, sometimes in the absence of shoulder symptoms. Localized myalgias are commonly caused by muscle strain. Acute compartment syndrome, raised pressure in a closed fascial space, is a surgical emergency that usually occurs in the setting of trauma,[88] although a chronic form occurs in athletes.[28] Medial tibial stress syndrome (shin splints) is also associated with athletic training, and causes symptoms similar to those of stress fracture.[28] Other causes of bone pain include malignancy and osteomyelitis.[89] Questions have been raised about the association between vitamin D deficiency and chronic musculoskeletal pain including lower extremity pain, but vitamin D supplementation has not been associated with pain relief.[90,91]

SUMMARY

Leg pain is common, and patients may have more than one cause. Although simple questionnaires or descriptors (eg, cramps, aching) are inadequate to distinguish between etiologies, history plays a key role in diagnosis. Timing and triggers of symptoms as well as lateralization can narrow the differential. Nocturnal symptoms are likely to be cramps, RLS, or DSP. Exertional symptoms suggest PAD, whereas symptoms caused by standing may be LSS or venous insufficiency. DVT and radiculopathy are usually unilateral, whereas DSP, RLS, and statin myalgia tend to be bilateral.

Fortunately, few of the diagnoses discussed constitute medical emergencies. DVT, acute compartment syndrome, pyomyositis, and malignancy all require prompt diagnosis and treatment. However, PAD (without rest pain, ulceration, or gangrene) is unlikely to progress rapidly, and routine radiculopathy and spinal stenosis (with no cauda equina syndrome or rapidly progressive neurologic deficit) can safely be managed conservatively. That said, accurate diagnosis of leg discomfort can afford patients a prognosis and, in some cases, effective therapy.

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