Autonomic dysfunction: A guide for FPs

Impotence, bladder dysfunction, GI symptoms, and orthostatic hypotension can signal autonomic dysfunction. Here’s what you’ll see and how to respond.

Signs and symptoms of autonomic dysfunction commonly present in the primary care setting. Potential causes of dysfunction include certain medications and age-related changes in physiology, as well as conditions such as diabetes mellitus, multiple sclerosis, and Parkinson’s disease (TABLE 1). This evidence-based review details common manifestations of autonomic dysfunction, provides a streamlined approach to patients presenting with symptoms, and reviews appropriate step-wise management.

When a delicate balance is disrupted

The autonomic nervous system provides brisk physiologic adjustments necessary to maintain homeostasis. Physiologic functions impacted by the central nervous system include: heart rate, blood pressure (BP), tone of the bladder sphincter and detrusor muscle, bowel motility, bronchodilation and constriction, pupillary dilation and constriction, sweating, catecholamine release, erection, ejaculation and orgasm, tearing, and salivation.1

Disorders of the autonomic system may result from pathologies of the central or peripheral nervous system or from medications including some antihypertensives, selective serotonin-reuptake inhibitors (SSRIs), and opioids.1 Such disorders tend to be grouped into one of 3 categories: those involving the brain, those involving the spinal cord, and autonomic neuropathies.1

The source of dysautonomia can often be determined by clinical context, coexisting neurologic abnormalities, targeted testing of the autonomic nervous system, and neuroimaging.1

Worrisome symptoms prompt a visit

A thorough history is critical to zeroing in on a patient’s complaints and ultimately providing treatment that will help manage symptoms.
When patient complaints are suggestive of autonomic dysfunction, a review of systems should include inquiry about lightheadedness, abnormal salivation, temperature changes of the extremities, gastrointestinal issues (vomiting, constipation, or diarrhea), and symptoms of presyncope/syncope or urinary or sexual dysfunction.1 The physical exam should include recordings of BP and heart rate in the supine and standing positions and a complete neurologic examination.1 Findings will typically point to one or more common complications.

Common complications of autonomic dysfunction
Complications of autonomic dysfunction include impotence, bladder dysfunction, gastrointestinal (GI) dysfunction, and orthostatic hypotension and vasomotor abnormalities. A less common condition—autonomic dysreflexia, which is a distinct type of autonomic dysfunction, and a true medical emergency—is also important to keep in mind.

Impotence
Autonomic neuropathy is a common cause of impotence and retrograde ejaculation. Loss of early morning erections and complete loss of nocturnal erections often have an etiology related to vascular disease and/or autonomic neuropathy. In addition, poor glycemic control and vascular risk factors appear to be associated with the development of diabetic autonomic neuropathy.2

Development of an erection requires an increase in parasympathetic activity and a decrease in sympathetic output. Nocturnal penile tumescence testing has been used to infer parasympathetic damage to the penis in men with diabetes who do not have vascular disease.3

First and second-line agents. Phosphodiesterase-5 inhibitors (eg, sildenafil, tadalafil, vardenafil) have demonstrated efficacy in improving the ability to achieve and maintain erections in patients with autonomic dysfunction, including diabetic autonomic neuropathy.4-6 Second-line therapies with proven efficacy include intraurethral application and intracavernosal injections of alprostadil.7,8

Bladder dysfunction
Sympathetic activity increases bladder sphincter tone and inhibits detrusor activity, while the parasympathetic nervous system increases detrusor activity and decreases sphincter tone to aid in voiding.1 Disrupted autonomic activity can lead to urinary frequency, retention, and hesitancy; overactive bladder; and incontinence.1 Brain and spinal cord disease above the level of the lumbar spine results in urinary frequency and small bladder volumes, whereas diseases involving autonomic nerve fibers to and from the bladder result in large bladder volumes and overflow incontinence.9

Patients presenting with lower urinary tract symptoms require a comprehensive evaluation to rule out other pathologies, as the differential for such symptoms is broad and includes infection, malignancies, interstitial cystitis, and bladder stones. The initial evaluation of lower urinary tract symptoms should include a history and physical exam including that of the abdomen, pelvis, and neurologic system. Lab work should assess renal function and blood glucose, and should
include urinalysis and culture to rule out infection and/or hematuria. A prostate-specific antigen (PSA) test may be appropriate in men with a life expectancy >10 years, after counseling regarding the risks and benefits of screening.

**Anticholinergic drugs** with antimuscarinic effects, such as oxybutynin, may be used to treat symptoms of urge incontinence and overactive bladder. They work to suppress involuntary contractions of the bladder’s smooth muscle by blocking the release of acetylcholine. These medications relax the bladder’s outer layer of muscle—the detrusor. Such medications often have a number of anticholinergic adverse effects, such as dry mouth and constipation, sometimes leading to discontinuation. A post-void residual (PVR) test may be helpful in guiding management. For example, caution should be used in patients with elevated PVRs, as anticholinergics can worsen urinary retention.

**Beta-3 agonists** (e.g., mirabegron) are a novel class of medications used to treat overactive bladder. These medications act to increase sympathetic tone in the bladder. Because they have the potential to raise BP, monitor BP in patients taking these agents. In addition, monitor patients taking antimuscarinics or beta-3 agonists for the development of urinary retention.

**Other tests, treatments.** Urodynamic testing is recommended for patients who fail to respond to treatment. Combining behavioral therapy with medication has been shown to be effective in patients with urge incontinence. Botulinum toxin type A, injected directly into the detrusor muscle, can be as effective as medication in patients with urinary urge incontinence.

**Detrusor underactivity** is defined as contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal timespan. This diagnosis is typically made using urodynamic testing. PVRs ≥150 mL are considered evidence of urinary retention. Overflow incontinence can result from detrusor underactivity.

Consider a trial of a cholinergic agonist, such as bethanechol, in patients with urinary retention. Some patients will require intermittent straight catheterization or chronic indwelling foley or suprapubic catheters to void.

**Gastrointestinal dysfunction**

In patients with diabetes, GI autonomic neuropathy can result in altered esophageal motility leading to gastroesophageal reflux disease (GERD) or dysphagia, gastroparesis, or diabetic enteropathy. Gastroparesis often presents as nausea, vomiting, and bloating. It may be diagnosed via gastric emptying studies (scintigraphy), and often requires a multidimensional approach to treatment.

**Management.** Food may be chopped or pureed to aid in digestion. Metoclopramide is the most commonly used prokinetic agent, but avoid its use in patients with parkinsonism. In more severe cases, consider adding domperidone and erythromycin as prokinetic agents. Recommend antiemetics, such as diphenhydramine, ondansetron, and prochlorperazine for management of nausea and vomiting. Severe cases of gastroparesis may merit a venting gastrostomy tube for decompression and/or feeding via a jejunostomy tube. Impaired intestinal mobility may lead to stasis syndrome, causing diarrhea.

**Hypermobility** caused by decreased sympathetic inhibition can also contribute to diarrhea. Altered anal sphincter function tone may contribute to fecal incontinence. Management should focus on balancing electrolytes, maintaining adequate fluid intake, and relieving symptoms. Consider antidiarrheals such as loperamide, but use them with caution to avoid toxic megacolon. Patients with constipation due to spinal cord lesions may benefit from a routine bowel regimen. To provide predictable defecation, advise patients to begin by inserting a stimulant rectal suppository. Follow with gentle digital stimulation of the distal rectum for one minute or less. They’ll need to repeat the process every 5 to 10 minutes until stool...
evacuation is complete. A forward-leaning position may assist with evacuation. It is helpful to perform this routine at the same time each day.\textsuperscript{17}

**Orthostatic (postural) hypotension**

The autonomic nervous system plays an important role in maintaining BP during positional changes. The sympathetic nervous system adjusts the tone in arteries, veins, and the heart. Baroreceptors located primarily in the carotid arteries and aorta, are highly sensitive to changes in BP. When the baroreceptors sense the slightest drop in pressure, a coordinated increase in sympathetic outflow occurs. Arteries constrict to increase peripheral resistance and BP, and heart rate and contractility increase, all in an attempt to maintain BP and perfusion.\textsuperscript{18}

- The most common causes of orthostatic hypotension are not neurologic in origin,\textsuperscript{9} but rather involve medications, hypovolemia, and impaired autonomic reflexes. The condition is common in the elderly, with one study demonstrating a prevalence of 18.2\% in those $\geq 65$ years.\textsuperscript{19}

Orthostatic hypotension may present with dimming or loss of vision, lightheadedness, diaphoresis, diminished hearing, pallor, and weakness. As a result, it is a risk factor for falls. Syncope results when the drop in BP impairs cerebral perfusion. Signs of impaired baroreflexes are supine hypertension, a heart rate that is fixed regardless of posture (the heart rate should increase upon standing), postprandial hypotension, and an excessively high nocturnal BP.\textsuperscript{1}

- Orthostatic hypotension is diagnosed when, within 3 minutes of quiet standing after a 5-minute period of supine rest, one or both of the following is present: at least a 20 mm Hg-fall in systolic pressure or at least a 10 mm Hg-fall in diastolic pressure.\textsuperscript{20} Soysal et al demonstrated that such a drop in BP, measured one minute after standing, is adequate and effective for diagnosing orthostatic hypotension in the elderly.\textsuperscript{21}

- Nonpharmacologic management. Recognition and removal of medications that can exacerbate orthostatic hypotension is the first step in managing the condition. Such medications include diuretics, beta-blockers, alpha adrenergic blockers, vasodilators, antipsychotics, antidepressants (SSRIs, trazodone, monoamine oxidase inhibitors, and tricyclic antidepressants), phosphodiesterase inhibitors, narcotics, and antiparkinsonian medications.\textsuperscript{22}

  Lifestyle interventions, such as having the patient arise slowly and maintain good hydration, can be helpful. Eating smaller, more frequent meals may also help if the orthostatic hypotension is triggered postprandially. Compressive stockings can help limit venous pooling in the lower extremities and improve venous return. Tensing the legs by crossing them while standing on both feet has been shown to increase cardiac output and BP.\textsuperscript{23} An aerobic exercise regimen of walking or stair climbing 30 to 45 minutes/day 3 days/week for 6 months was shown to eliminate symptoms of orthostasis on tilt table testing in elderly patients with cardiac deconditioning, as opposed to chronic autonomic failure.\textsuperscript{24}

The reduction in central blood volume associated with autonomic insufficiency (due to increased urinary sodium and water excretion) can be lessened by increasing sodium and water intake.\textsuperscript{25-27}

- Pharmacotherapy. Fludrocortisone acetate, a synthetic mineralocorticoid, is the medication of first choice for most patients with orthostatic hypotension whose symptoms are not adequately controlled using nonpharmacologic measures,\textsuperscript{28} but keep in mind that treating orthostatic hypotension with fludrocortisone is an off-label use of the medication.

  Monitor patients taking fludrocortisone for worsened supine hypertension and edema. Also, check their serum potassium levels one to 2 weeks after initiation of therapy and after dose increases. Frequent home monitoring of BP in sitting, standing, and supine positions may be helpful in assessing response to therapy.

  If the patient remains symptomatic despite therapy with fludrocortisone, consider adding an alpha-1 adrenergic agonist, such as midodrine. Avoid prescribing midodrine, however, for patients with advanced cardiovascular disease, urinary retention, or uncontrolled hypertension.\textsuperscript{29}
Autonomic dysreflexia: A medical emergency

Autonomic dysreflexia, a medical emergency that must be recognized immediately, is a distinct type of autonomic dysfunction seen in patients with spinal cord injury at or above the T6 level. It is a condition of uncontrolled sympathetic response secondary to an underlying condition such as infection, urinary retention, or rectal distention.

Common symptoms include headache, significant hypertension, flushing of the skin, and diaphoresis above the level of injury. In addition, a review of systems should screen for fever, visual changes, abnormalities of the cardiovascular system, syncope, bowel and bladder symptoms, and sexual dysfunction.

Patients demonstrating autonomic dysreflexia should be placed in the upright position to produce an orthostatic decrease in BP. Patients should be evaluated to identify any reversible precipitants, such as urinary retention or fecal impaction. Severe attacks involving hypertensive crisis require prompt transfer to the emergency department. Sublingual nifedipine or an intravenous agent, such as hydralazine, may be used to lower BP.

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References