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451 Disorders of the Autonomic Nervous System

■ ■FURTHER READING Anheim M et al: The autosomal recessive cerebellar ataxias. N Engl J

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Disorders of the

Autonomic Nervous System The autonomic nervous system (ANS) has a large central nervous sys tem (CNS) organization and an extensive peripheral nervous system (PNS) network that innervates and influences all organ systems. As such, it is important in securing normal homeostasis. The ANS has three major components: parasympathetic, sympathetic, and enteric. The parasympathetic component has mainly a craniosacral localiza tion (brainstem and sacral cord), while the sympathetic component has mainly a thoracolumbar localization (first thoracic to second lumbar segments). ANS neurons of these components project thinly myelin ated fibers to autonomic ganglia, where they synapse with postgangli onic, mainly unmyelinated fibers that innervate the respective target organs. The enteric nervous system (ENS) has its own set of autonomic neurons and neurotransmitters but is heavily regulated by the central and peripheral autonomic nervous systems. The ANS also sensitizes endocrine organs to the effect of hormones, influencing how hormonal balances may affect neurologic diseases. The classification of autonomic dysfunction (or dysautonomia) can be based on the impaired component (sympathetic, parasympathetic, or enteric), but a more practical clinical approach is based on organ specificity: heart, blood vessels, sweat glands, pupils, gastrointestinal, and genitourinary, either in isolation or in any potential combination. The time course of the development of dysautonomia (acute, subacute, or chronic; progressive or static) is especially useful in the differential etiologic diagnosis. The ANS functions

as a reflex circuit, using the sensory and sen sorial feedback from the organs to modulate the ANS output and maintain homeostasis. This requires exquisite integration of the cen tral ANS, peripheral ANS, and target organs. In the CNS, autonomic circuits operate at several levels: cerebral supratentorial, cerebral infratentorial, and spinal. Supratentorial areas include the insular cor tex, prefrontal cortex, limbic lobe located on the medial surface of the cerebral hemispheres, hypothalamus, and hypothalamic-pituitary axis. Infratentorial areas are mainly the nucleus tractus solitaries (NTS), dorsal motor nucleus of the vagus (DMV) and nucleus ambiguous (NA). Spinal areas are in the intermediate lateral horns (IML) of the spinal cord gray matter between the first thoracic segment and the fourth sacral segment. Descending CNS information to the brainstem and IML allows the CNS to modulate autonomic activity. Peripheral, visceral, spinal, and brainstem afferent information conveyed to the CNS is also important in influencing autonomic function in health and

disease. ANS dysfunction may explain many symptoms related to the aging process and various degenerative neurologic disorders, such as Parkinson’s disease, multiple system atrophy, Lewy body disease, and pure autonomic failure. It features prominently in various autoimmune disorders, particularly autoimmune autonomic ganglionopathy and certain paraneoplastic disorders. ANS dysfunction in a more restricted form is present in various cyclical disorders such as migraine, cyclic vomiting, and other circadian rhythm disorders. It plays an important role in the genesis of various conditions of orthostatic intolerance (OI) including orthostatic hypotension (OH), postural orthostatic tachycar dia syndrome (POTS), and syncope. A detailed discussion of syncope can be found in Chap. 23. ANATOMIC, BIOCHEMICAL, AND PHARMACOLOGIC ORGANIZATION Connections between ANS centers in the cerebral cortex and brain stem coordinate autonomic outflow and their integration with emo tional and higher mental functions. The preganglionic parasympathetic neurons leave the CNS in the third, seventh, ninth, and tenth cranial nerves as well as the second to fourth sacral nerves. The preganglionic sympathetic neurons exit the spinal cord between the first thoracic and the second lumbar segments (Fig. 451-1). The autonomic ganglia reside outside the CNS. The sym pathetic ganglia are located in paravertebral and prevertebral ganglia, while the parasympathetic ganglia are located near, or sometimes within, the target organs. Responses to sympathetic and parasympa thetic stimulation are frequently antagonistic (Table 451-1), allowing fine-tuning of autonomic responses. In general, increased sympathetic activity leads to the “fight or flight” response, while parasympathetic activity leads to the “rest and digest” response. Biochemically, acetylcholine (ACh) is the preganglionic neurotrans mitter for both sympathetic and parasympathetic divisions of the ANS as well as the postganglionic neurotransmitter of the parasympathetic neurons; all preganglionic receptors are nicotinic, while postgangli onic receptors are muscarinic in type. Norepinephrine (NE) is the neurotransmitter of postganglionic sympathetic neurons, except for sympathetic cholinergic neurons innervating the eccrine sweat glands where the neurotransmitter is also ACh. As stated above, the ENS has a large number of neurons organized in plexuses. Meissner’s (submucosal) plexus, Auerbach’s (myenteric) and interstitial cells of Cajal (circular muscular) compose the majority of the ENS; they contain numerous neurotransmitters. Parasympathetic control of the gastrointestinal system is mediated through the cranio spinal nerves (vagus and S2–S4 nerves), while sympathetic control is mediated through the thoracolumbar (T1–L2) nerves. CLINICAL EVALUATION Disorders of the ANS are rather common and can occur with either CNS or PNS pathology that disrupts the afferent limb, CNS processing center, efferent limb, or any combination of these. It is also important to recognize that clinical manifestations can result from decreased function, overactivity, or dysregulation of autonomic

circuits. The evaluation begins by taking an accurate and complete auto nomic medical history. The chief complaint and history of present illness should be sought from the patient, assisted by family members or significant others when necessary. Records from previous hospi talizations and test results are useful but cannot substitute for direct history taking. It is important to obtain the sequence of symptoms as accurately as possible. Antecedent events such as a viral illness or surgi cal procedure followed by subacute OI suggests an autoimmune cause, while a history of frequent fainting since childhood or adolescence favors a congenital or genetic condition. Therefore, a detailed family history is often essential, particularly in younger patients. In a patient with POTS, which occurs mainly in young women, it is important to ask privately about emotional or physical abuse in childhood. Physical deconditioning often exacerbates chronic OI and POTS. A prior his tory of irradiation to the neck in a patient with labile blood pressure and OI suggests arterial baroreflex failure due to injury to the carotid sinus baroreceptors.

III Ciliary ganglion Eye VII IX X T1 T2 T3 T4 T5 T6 T7 T8 T9
T10
T11
T12 L1 L2 S2 S3 S4
Pelvic splanchnic nerve FIGURE 451-1 Schematic representation of the autonomic nervous system. (Reproduced with permission from R Snell: Clinical Neuroanatomy, 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2009.) Like other medical histories, it is important to determine exac erbating and alleviating factors. In patients with OI, the positional nature of symptoms (standing vs supine or sitting) can be a key clue to diagnosis. Patients with neurogenic OH are often more symptomatic in the morning, after exercise particularly in the heat, or after eating a large meal, especially with alcohol. Patients with POTS may feel worse when standing in a warm shower and notice reddish or purplish feet

Parasympathetic nerves Preganglionic fibers Postganglionic fibers Sympathetic nerves Preganglionic fibers Postganglionic fibers Lacrimal gland Submandibular and sublingual salivary glands CHAPTER 451 Otic g. Parotid gland Disorders of the Autonomic Nervous System Heart Lungs Celiac g. Stomach Small intestine Sup. mes. g. Suprarenal gland Kidney Renal g. Inf. mes. g. Colon Rectum Urinary bladder Sex organs in that situation. However, given the widespread autonomic network underlying many dysautonomic states, these conditions are often mul tisystemic, and specific symptoms can vary from day to day. A review of autonomic symptoms begins with questions about OI (lightheadedness, dizziness, orthostatic weakness or dyspnea, orthostatic neck and shoulder discomfort, orthostatic headache), a history of supine hypertension, unpredictable blood pressure swings,

TABLE 451-1 Effects of Sympathetic and Parasympathetic Systems on Various Effector Organs SYMPATHETIC PARASYMPATHETIC Pupil Pupillodilation (alpha) Pupilloconstriction Accommodation Decreased Increased Heart Positive chronotropic effect (beta) Positive inotropic effect (beta) Negative chronotropic effect Negative inotropic effect Arteries Vasoconstriction (alpha) Vasodilation (beta) Vasodilation Veins Vasoconstriction (alpha) Vasoconstriction (beta) Tracheobronchial tree Bronchodilation (beta) Bronchoconstriction Increased bronchial gland secretions Gastrointestinal tract Decreased motility (beta) Contraction of sphincters (alpha) Increased motility Relaxation of sphincter PART 13 Neurologic Disorders Bladder Detrusor relaxation (beta) Contraction of sphincter (alpha) Detrusor contraction Relaxation of sphincter

Salivary glands Scant, thick, viscid saliva (alpha) Copious, thin, watery saliva Skin Piloerection (cutis anserina) No piloerection Sweat glands Increased secretion (cholinergic) Decreased secretion Genitalia Ejaculation Ejaculation/Erection Adrenal medulla Catecholamine release Glycogen Glycogenolysis (alpha and beta) Lipolysis (alpha and beta) Glycogen synthesis Source: Reproduced with permission from WW Campbell: The autonomic nervous system, in DeJong's The Neurologic Examination, 8th ed. Wolters Kluwer, 2020. or syncopal episodes. Gastrointestinal symptoms may resemble those of irritable bowel syndrome (constipation, diarrhea, or both), but also constant nausea and bloating, unexplained vomiting, or dumping syn drome may be present, both in diabetics and in others. Genitourinary symptoms include dysuria, incontinence, urgency, and male erectile dysfunction. Sweating abnormalities (dry skin, excessive sweating) and body temperature changes reflect disordered thermoregulation and heat dissipation. Sicca syndrome may resemble that of Sjögren syndrome. Blurred vision from dark to light suggests slow, tonic pupil lary dilation. Pertinent nonautonomic symptoms such as acroparesthesias or burning feet (and hands) suggest an autonomic small-fiber neuropa thy. Impaired olfaction, impaired balance, abnormal movements, and abnormal sleep behavior (apnea, stridor, or excessive moving and talk ing during sleep known as dream enactment behavior) are red flags for a degenerative neurologic extrapyramidal disorder. A complete listing of all prescribed drugs, over-the-counter medica tions, herbal remedies, and dietary supplements is important because they can affect autonomic function and may produce unexpected adverse events. For instance, certain diet supplements have sympa thomimetic activity and cause unexpected hypertension, tachycardia, or both. Physical examination begins by obtaining full vital signs, including supine blood pressure and heart rate, followed by orthostatic blood pressure values at 1 and 3 min after rising from a seated position. An abnormal body temperature, either hyperthermia or hypothermia, may be a clue to a systemic or endocrine illness. Next comes the inspection of the limbs, looking for changes in the feet (pes cavus or planus), vasomotor color changes in the distal limbs, neuropathic foot or toe ulcers, scoliosis, chest deformity (pectus excavatum or carinii), hyper mobility, skin elasticity, arachnodactyly, an abnormal pattern of sweat ing or hair distribution, or angiokeratoma (Fabry's disease). Head and neck evaluation begins with a careful pupillary examination in a dark room, looking for asymmetry, miosis, mydriasis, reaction to light and accommodation, and rate and symmetry of redilation. A high-arched

palate is present in some patients with OI and Ehlers-Danlos syndrome (Chap. 425). The tongue's appearance (smooth vs normal) and size (macroglossia suggests amyloidosis) should be noted. For patients in whom a neurologic cause is likely, a complete evalu ation of the cranial nerves, strength and muscle tone, reflexes, sensory function including small-fiber modalities (pinprick, temperature), cer ebellar function, and gait is important (Chap. 433). This may require a neurologic referral if the primary care physician is uncomfortable with the assessment. LOCALIZATION Once the history and examination are complete, an initial localization is usually possible, based on a working knowledge of the anatomy and pharmacology of ANS components. For example, parasympathetic dysfunction is mainly cholinergic. Patients will report dry mouth and constipation, urinary retention, and erectile failure in men. On the other hand, sympathetic dysfunction is mainly adrenergic (nor epinephrine, epinephrine, dopamine) and symptoms and signs of OI predominate, given the prominent effect of these neurotransmitters on cardiac function and vasomotor tone. These patients will report lightheadedness, dizziness, faintness, visual changes, and a need to sit down. Muscarinic dysfunction leads to reduced sweating, hyperthermia, reduced salivation and lacrimation (sicca syndrome), mydriasis with blurred vision, slow gastrointestinal motility, and

urinary retention. Tachycardia and arrhythmias are less common. Some CNS symptoms such as delirium and hallucinations may occur. Adrenergic dysfunction presents with excessive sweating, vasomo tor changes, irritable bowel syndrome, dysuria and stress incontinence. Tachycardia and arrhythmias are common. Miosis or mydriasis may occur, usually without blurred vision. Some CNS symptoms are panic, anxiety, and mood disorders. Certain features favor preganglionic versus postganglionic localiza tion. Preganglionic disorders are more likely to cause body temperature dysregulation, syncope and POTS, sleep disturbances, and autonomic storms. Postganglionic disorders are more likely in the presence of acral pain, acral anhidrosis, severe OH, and severe gastrointestinal or urinary dysmotility. However, overlap may occur as some pathologic conditions involve both preganglionic and postganglionic systems; examples include autoimmune, paraneoplastic, and neurodegenerative disorders. LABORATORY EVALUATION Testing begins by obtaining basic blood tests (complete blood count with differential, comprehensive metabolic panel, erythrocyte sedi mentation rate). It is important to check iron, ferritin, vitamin B12, and vitamin D levels as well as folic acid. In patients with gastrointestinal distress, particularly with significant weight loss, measurement of vari ous nutritional factors and vitamins is important, including less com mon ones such as thiamine, vitamin B6, niacin, riboflavin, vitamin C, vitamin E, serum copper, coenzyme Q10, and carnitine levels. A search for endocrine disorders such as diabetes, thyroid disease, or disorders of adrenal cortical (cortisol) and medullary (catecholamine) function may be necessary, as well as 5-hydroxyindoleacetic acid (5-HIAA) to look for carcinoid tumors. In patients with small-fiber neuropathy and normal hemoglobin A1c, a 2-h glucose tolerance test is necessary, as glucose intolerance is a rather frequent cause of isolated small-fiber neuropathy in the absence of overt diabetes. In patients with OI, supine and upright catecholamine levels can provide useful information. In patients with central or preganglionic adrenergic dysautonomia, supine catecholamine levels tend to be normal but fail to rise significantly in the upright position; the normal healthy response is a doubling or greater. In patients with peripheral or postganglionic adrenergic dys autonomia, supine catecholamine levels tend to be low and also fail to rise significantly in the upright position. In some acquired autonomic disorders, rheumatologic test screen ing, particularly for Sjögren’s syndrome (Chap. 373), scleroderma (Chap. 372), and mixed connective tissue disease (Chap. 372), is use ful. If the bedside examination or autonomic testing shows evidence

for a peripheral autonomic neuropathy, serum free light chains and protein electrophoresis to look for paraproteinemia is important, as it may be the sign of early primary amyloidosis (Chap. 117). In probable acquired autonomic disorders, serologic tests to check for autoimmune markers are indicated, including antibodies to the ganglionic ACh nicotinic receptor (see “Autoimmune Autonomic Ganglionopathy,” below), voltage-gated potassium and calcium P/Q channel, plexin, and glutamic acid decarboxylase (GAD). If a paraneoplastic etiology is suspected, testing for anti-Hu, anti-CRMP5, anti-amphiphysin, or other autoantibodies may also be indicated (Chap. 99). If there is a history of infection, appropriate serologic tests can be requested (e.g., HIV, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus, cytomegalovirus). In young patients or those with a positive family history, testing for porphyria (Chap. 428) and Fabry’s disease (Chap. 429) is important, as these conditions are now treatable (Table 451-2). TABLE 451-2 Classification of Clinical Autonomic Disorders I. Autonomic Disorders with Brain Involvement A. Associated with multisystem degeneration

1. Multisystem degeneration: autonomic failure clinically prominent a. Multiple-system atrophy (MSA) b. Parkinson’s disease with autonomic failure c. Diffuse Lewy body disease with autonomic failure
2. Multisystem degeneration: autonomic failure clinically not usually prominent a. Parkinson’s disease without autonomic failure b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease, fragile X syndrome [FXTAS]) B. Unassociated with multisystem degeneration (focal CNS disorders)
3. Disorders mainly due to cerebral cortex involvement a. Frontal cortex lesions causing urinary/bowel incontinence b. Focal seizures (temporal lobe or anterior cingulate) c. Cerebral infarction of the insula
4. Disorders of the limbic and paralimbic circuits a. Limbic encephalitis b. Autonomic seizures c. Shapiro’s syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia) II. Autonomic Disorders with Spinal Cord Involvement A. Traumatic quadriplegia B. Syringomyelia C. Subacute combined degeneration D. Multiple sclerosis and neuromyelitis optica III. Autonomic Neuropathies A. Acute/subacute autonomic neuropathies a. Subacute autoimmune autonomic ganglionopathy (AAG) b. Subacute paraneoplastic autonomic neuropathy c. Guillain-Barré syndrome d. Botulism e. Porphyria f. Drug-induced autonomic neuropathies—stimulants, drug withdrawal, vasoconstrictor, vasodilators, beta-receptor antagonists, beta-agonists g. Toxin-induced autonomic neuropathies h. Subacute cholinergic neuropathy Abbreviations: BP, blood pressure; CNS, central nervous system; HR, heart rate; OH, orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome.

AUTONOMIC EVALUATION TESTS The most commonly employed autonomic tests evaluate cardiovascu lar function.

■ ■HEART RATE VARIATION TO DEEP BREATHING This tests the parasympathetic cardiovascular reflexes mediated via the vagus nerve. The patient is instructed to breathe deeply at a rate of 6 breaths/min, and the acceleration and deceleration of the heart rate accompanying the inspiratory/expiratory cycle is calculated and averaged. The score is the average of the heart rate variability, or the expiratory to inspiratory ratio (Fig. 451-2). The ratio decreases gradu ally with age and is therefore age-corrected. ■ ■VALSALVA MANEUVER This test is performed in the supine position. The patient blows into a closed mouthpiece to increase the intrathoracic pressure by CHAPTER 451 3. Disorders of the hypothalamus a. Thiamine deficiency (Wernicke-Korsakoff syndrome) b. Diencephalic syndrome c. Neuroleptic malignant syndrome d. Serotonin syndrome e. Fatal familial insomnia Disorders of the Autonomic Nervous System f. Antidiuretic hormone (ADH) syndromes (diabetes insipidus, inappropriate ADH secretion) g. Disturbances of temperature regulation (hyperthermia, hypothermia) h. Disturbances of sexual function i. Disturbances of appetite j. Disturbances of BP/HR and gastric function k. Horner’s syndrome 4. Disorders of the brainstem and cerebellum a. Posterior fossa tumors b. Syringobulbia and Arnold-Chiari malformation c. Disorders of BP control (hypertension, hypotension) d. Cardiac arrhythmias e. Central sleep apnea f. Baroreflex failure g. Horner’s syndrome h. Vertebrobasilar and lateral medullary (Wallenberg’s) syndromes i. Brainstem encephalitis E. Amyotrophic lateral sclerosis (mild, late) F. Tetanus G. Stiff-person syndrome H. Spinal cord tumors B. Chronic peripheral autonomic neuropathies

1. Small fiber neuropathy, including cryptogenic sensory polyneuropathy (CSPN)
2. Combined sympathetic and parasympathetic failure a. Amyloid b. Diabetic autonomic neuropathy c. AAG (paraneoplastic and idiopathic) d. Sensory neuronopathy with autonomic failure e. Fabry's disease f. Diabetic, uremic, or nutritional deficiency g. Familial dysautonomia (Riley-Day syndrome) h. Hereditary sensory and autonomic neuropathy i. HIV-related autonomic neuropathy j. Geriatric dysautonomia (age >80 years)
3. Disorders of orthostatic intolerance: OH; POTS; reflex syncope; prolonged bed rest; space flight; chronic fatigue

Heart rate (Beats/Min)

A 01:00 02:00 03:00 02:30 01:30

00:30

PART 13 Neurologic Disorders Heart rate (Beats/Min)

03:30

02:10 02:20 02:30 02:40 02:50 Time scale (Min:Sec) B FIGURE 451-2 Examples of normal (A) and reduced (B) heart rate variability to deep breathing.

> 40 mmHg for 15 s. During blowing, there is a decrease in venous return to the heart, leading to a fall in blood pressure and an associ ated compensatory tachycardia. Reduced blood pressure induces a compensatory peripheral sympathetic vasoconstriction in the lower extremities, which stops the blood pressure fall and reverses it close to baseline. Following release of the effort, blood pressure rises due to increased cardiac filling from the venous return, along with persistent sympathetic vasoconstriction. This leads to transient hypertension (an overshoot response) that stimulates the aortic and carotid barorecep tors leading to reflex bradycardia. The Valsalva ratio is the ratio of the higher to the lower heart rate and is a measure of the parasympathetic arm of the baroreflex. The magnitude of the drop in blood pressure, and of recovery in the overshoot phase, produces an adrenergic index score that, along with the blood pressure recovery time, is a marker of the sympathetic arm of the baroreflex (Fig. 451-3). The heart rate variation to deep breathing and the Valsalva ratio are diminished in most patients with autonomic failure, including diabetes and α-synuclein disorders and also in patients who take anticholinergic medications. ■ ■TILT TABLE TESTING This test of great value for patients with all syndromes of OI, with or without syncope. Many autonomic laboratories are equipped with spe cial devices and a finger cuff that enables the accurate reproduction of beat-to-beat arterial waveforms. The tilt test is an excellent test of sym pathetic vasomotor and cardiovascular innervation, as it detects OH in all

> its forms, as well as excessive orthostatic tachycardia (Fig. 451-4). When syncope occurs, testing allows differentiation between the vari ous types (i.e., vasovagal, vasodepressor, and cardiodepressor syncope). Tilt Table Testing for Recurrent Syncope When an initial phase of tilt at an angle of 60–70° for 30–40 min is negative, pharma cologic provocation of syncope (with intravenous, sublingual, or spray nitroglycerin, or intravenous isoproterenol) can be used. This increases

03:00 03:10 03:20 the sensitivity of testing, at the expense of specificity (i.e., some patients with normal sympathetic function may also faint after administration of these drugs). ■ ■SUDOMOTOR FUNCTION TESTING Sweating is secondary to the release of ACh from sympathetic postgan glionic fibers. The quantitative sudomotor axon reflex test (QSART) measures regional ACh-induced sweating. The test is usually per formed at four different sites (forearm, proximal leg, distal leg, and foot) to provide information on both the extent and distribution of postganglionic sudomotor impairment (Fig. 451-5). A low or absent response indicates a lesion of the postganglionic sudomotor axon. If the equipment necessary to perform the test is not available, sym pathetic skin responses recorded from the foot and the hand using standard nerve conduction equipment can be used, although results obtained in this manner may be less sensitive and specific. As a gen eral rule, autonomic or small-fiber neuropathies often lead to reduced sweating in the feet. The thermoregulatory sweat test (TST) is a qualita tive measure of global sweat production in response to an elevation of body temperature under controlled conditions. An indicator powder dusted on the anterior surface of the forehead and body changes color with sweat production in a hot and humid chamber. The pattern of color change measures the integrity of both preganglionic and postgan glionic sudomotor functions. A postganglionic lesion is present if both QSART and TST show absent sweating. In a preganglionic lesion, the QSART is preserved but TST shows anhidrosis. ■ ■SKIN BIOPSY Skin biopsies are commonly performed to diagnose small-fiber neu ropathies. These consist of small punch biopsy specimens, often 2–4 mm in diameter, stained for special axonal markers. This allows the identification of epidermal nerve fiber density as well as sudomo tor innervation density. Patients often undergo biopsies from two to four sites, usually from the distal and proximal lower extremity as well

Heart rate (Beats/Min)

09:00 10:00 10:15 10:30 09:15 09:30 09:45

Blood pressure (mmHg)

09:00 10:00 10:15 10:30 09:15 09:30 Time scale (Min:Sec) 09:45 A

Heart rate (Beats/Min)

02:00 03:00 03:15 03:30 03:45 02:15 02:30 02:45

Blood pressure (mmHg)

02:00 03:00 03:15 03:30 03:45 02:15 02:30 02:45 B FIGURE 451-3 A. The tracing shows a normal Valsalva ratio and blood pressure response. B. A low Valsalva ratio and abnormal blood pressure response are illustrated.

Expiratory pressure (mmHg)

CHAPTER 451

Expiratory pressure (mmHg)

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Expiratory pressure (mmHg)

Expiratory pressure (mmHg)

Time scale (Min:Sec)

Heart rate (Beats/Min)

TU 20:00 15:00

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Blood pressure (mmHg)

TU 15:00 20:00 TD A

Heart rate (Beats/Min)

tu

TU 10:00 15:00

Blood pressure (mmHg)

tu

10:00 20:00 25:00 15:00 TD TU B FIGURE 451-4 Examples of abnormal tilt responses. In each panel, the first tracing represents the heart rate, while the second represents the systolic, mean, and diastolic blood pressure responses. A. Progressive orthostatic hypotension leading to syncope. B. Neurogenic orthostatic hypotension (orthostatic hypotension without an adequate increase in heart rate). Notice the baseline supine hypertension (systolic blood pressure of 175 mmHg) due to associated baroreflex impairment. C. Postural orthostatic tachycardia syndrome (POTS). Notice the dramatic increase of the heart rate by >50 beats/min after tilt upward. TD, tilt downward; TU, tilt upward.

TD Time scale (Min:Sec) td TD 20:00 25:00 td Time scale (Min:Sec)

Heart rate (Beats/Min)

TU

TU 15:00

Blood pressure (mmHg)

TU

TU 15:00 C FIGURE 451-4 (Continued)

Sweat rate (nL/min)

t.i.m ON

00:00 05:00 10:00 15:00

Sweat rate (nL/min)

t.i.m ON

00:00 05:00 A FIGURE 451-5 A. Examples of normal (forearm, top tracing) and reduced (proximal leg, bottom tracing) quantitative sweat responses consistent with a mild, lengthdependent autonomic neuropathy. B. Normal (forearm, top tracing), reduced (proximal leg, middle tracing), and quasi-absent (distal leg, bottom tracing) quantitative sweat responses consistent with a length-dependent autonomic and small-fiber neuropathy. Tim ON, time when electrical stimulation is turned on to start iontophoresis of acetylcholine and induce sweating.

20:00 25:00 30:00 TD CHAPTER 451 Disorders of the Autonomic Nervous System 20:00 25:00 30:00 TD Time scale (Min:Sec) Forearm Prox Leg 10:00 15:00

Sweat Rate - Right Forearm

Sweat rate (µL)

20:50

00:00 04:10 Time 08:20 12:30 16:40 Sweat Rate - Right Proximal Leg

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20:50

00:00 04:10 Time 08:20 12:30 16:40

Sweat Rate - Right Distal Leg

Sweat rate (μL)

20:50

00:00 04:10 Time 08:20 12:30 16:40 B FIGURE 451-5 (Continued) as the forearm. The reduction in the number of nerve fibers and the pattern of reduction assist in establishing the diagnosis but also pro vide a clue to the underlying etiology, particularly when the fiber loss is not length-dependent. Skin biopsies are also useful in diagnosing autonomic dysfunction secondary to synucleinopathies, as at least one specimen may demonstrate phosphorylated α-synuclein inclusions in postganglionic sympathetic adrenergic and cholinergic nerve fibers. In these cases, a more proximal biopsy obtained near the cervical paraspi nal region can be a helpful diagnostic tool if it shows accumulation of α-synuclein (see specific disorders below). If all testing remains unrevealing, it is reasonable to consider a fat aspirate biopsy to check for amyloidosis. SPECIFIC CONDITIONS OF ANS DYSFUNCTION ■ ■ORTHOSTATIC HYPOTENSION OH is a common disorder with many underlying conditions. It can be debilitating, leading to fatigue, falls, syncope, cognitive impairment, and end-organ damage. OH increases with advancing age and is com monly associated with a variety of general medical, neurologic, and primary autonomic disorders including diabetes, heart failure, kidney failure, and neurodegenerative and autoimmune diseases.

Upon standing or with tilt testing, ~500–700 mL of blood shifts to peripheral venous vessels in the lower limbs and splanchnic bed, reduc ing venous return. In a healthy person, there is slight increase in heart rate and peripheral venoconstriction and arteriolar constriction that maintains systolic blood pressure (SBP) and increases slightly diastolic blood pressure (DBP). This normal response depends on interactions between multiple homeostatic systems, including baroreceptors, auto nomic afferents, central processing centers, autonomic efferents, and peripheral vascular sympathetic receptors. Classical OH is defined as a sustained reduction of SBP ≥20 mmHg or DBP ≥10 mmHg within 3 min of active standing or on a head-up tilt (HUT) test ≥60°. Variants of OH include smaller but symptom atic reductions in SBP when the supine SBP is low (90–100 mmHg) but drops well below this level with standing or tilt. In patients with hypertension, OH is defined as an orthostatic drop of SBP/DBP ≥30/15 mmHg. The prevalence of OH in the general population ranges from <5% below age 50 up to 20% above age 70. The diagnosis can be overlooked, as most patients are asymptomatic or have only minor symptoms. OH is associated with increased risk of falls, coronary heart disease, heart failure, stroke, and death. When the orthostatic compensatory heart rate (HR) increase exceeds 15 beats/min, OH is nonneurogenic. On the contrary, neurogenic OH

is associated with a blunted compensatory HR increase of <15 beats/ min, provided there are no other possible explanations, such as cardio active medications or intrinsic cardiac rhythm disturbances preventing an orthostatic HR increase. A more accurate way to diagnose neuro genic OH (NOH) is by dividing the HR increase by the fall in SBP (ΔHR/ΔSBP), as this metric provides a marker of cardiac baroreflex gain. A ratio <0.5 beats/min/mmHg after 3 min of standing (or tilt) more accurately indicates NOH. NOH is characterized by inadequate release of peripheral norepinephrine leading to impaired systemic vascular tone. The distinction is important because patients with NOH have a greater risk of mortality, approaching 44% over 30 months of follow-up, and exceeding 60% over 10 years. Furthermore, NOH can be associated with supine hypertension in patients with baroreflex impairment or autonomic failure, particularly in neurodegenerative

conditions. Clinical Presentation OH symptoms result from decreased blood flow to the brain. The most common symptom is lightheadedness on standing. Patients may report other orthostatic symptoms, such as palpitations, flushing, or pallor. More severe OH may lead to fainting or near-fainting. Triggers include bed rest (explaining the common occurrence upon waking up in the morning), food ingestion (particu larly a large meal with alcohol), fever, heat, exercise, hyperventilation, medications, sepsis, or surgery. Aging, long periods of exercise, and intensification of antihypertensive treatment sometimes trigger the symptoms. Patients with underlying cardiac conditions (heart failure, chronotropic insufficiency) often have an added cardiogenic compo nent to their OH. However, in the absence of triggers, many patients with mild OH remain asymptomatic, as cerebral autoregulation can compensate for mild swings in blood pressure and blood flow. Remark ably, in cases of chronic OH, particularly NOH, symptoms may remain quite mild in the face of significant blood pressure decrements. Many patients with chronic OH have indirect symptoms. Instead of lightheadedness and near fainting, they may report dizziness (usu ally feeling wobbly, falling, or rarely vertigo), wooziness, or orthostatic imbalance. They may report fatigue and tiredness. Some may complain of generalized weakness after prolonged standing or walking. Some report neck and shoulder discomfort (coat hanger syndrome) second ary to hypoperfusion of the cervical paraspinal and trapezius muscles. In others, orthostatic dyspnea, known as platypnea, develops second ary to hypoperfusion of the lung apex. Myocardial hypoperfusion may cause orthostatic angina. A few patients also report orthostatic headache that may be mistaken as low-pressure cerebrospinal fluid headache. OH can be classified into four functional classes. In functional class I, patients are asymptomatic but may show symptoms of OH including syncope and falls. In functional class II, symptoms occur weekly or monthly, with mild to moderate limitation of daily living. In functional class III, symptoms are more severe and frequent and markedly limit daily activities. In functional class IV, severe symptoms are daily, lead ing to significant disability. Other OH variants include initial, delayed, and postprandial OH. Initial OH is an exaggerated, abrupt decrease in blood pressure (>40 mmHg SBP and >20 mmHg DBP) within 15–30 s upon stand ing due to transient mismatch between cardiac output and systemic vascular resistance. This condition occurs almost exclusively in young subjects (adolescents and young adults) but may also occur in older patients treated with antihypertensive drugs. The magnitude of the initial OH is often less with tilt than it is with active standing. In delayed OH, SBP often remains steady for the first 3–5 min and then begins to decrease. In some cases, delayed OH does not appear until after 10 min of tilt. While the primary etiology in such cases may be secondary to medications, it often denotes some type of autonomic dysfunction, such as autonomic neuropathy. Postprandial OH is a blood pressure drop after eating. OH often appears within 2 h of a larger meal, particularly if there is a highcarbohydrate load or alcohol ingestion. In these conditions, the meal produces gastric and esophageal distension and an increase in the splanchnic blood volume. It is more frequent in elderly patients with

underlying neurologic conditions, particularly autonomic disorders. These patients sometimes faint after getting up from the dining table.

When OH is accompanied by baroreflex impairment, as seen with autonomic neuropathies or degenerative autonomic disorders, it can be associated with supine hypertension. In these patients, supine SBP during sleep may be higher than when they wake up in the morning, a pattern known as reverse dipping. Supine hypertension is a particular risk factor for end-organ damage (kidney, cardiac, or cerebrovas cular). Over time, affected individuals develop alterations in the

renin-angiotensin-aldosterone axis, leading to worse daytime OH by inducing pressure diuresis and volume loss during sleep. Management Management of OH includes nonpharmacologic and pharmacologic measures. Nonpharmacologic measures are essential and may be sufficient in earlier stage I OH. However, the physician needs to ascertain whether the patient is actually asymptomatic and safe. This begins by addressing possible identifiable confounders, such as medications interfering with cardiovascular reflexes (e.g., diuretics, antihypertensives, tricyclic antidepressants, antipsychotics, dopamine agonists). Comorbidities can include iron deficiency, vitamin B12 and D deficiencies, and frailty. Increasing fluid intake up to 3 L/d and salt intake to 2 g up to 3 times a day can expand plasma and blood volume and often improve orthostatic tolerance. It is important to monitor the patient's weight and blood pressure on this regimen. In some patients, it would be reasonable to check the 24-h urine sodium before and after initiation of the fluid and salt load. Other simple remedies include lower limb stockings applied before getting out of bed. An abdominal binder is also quite effective in reducing the amount of splanchnic blood pooling. Physical countermaneuvers, such as crossing the legs while standing, are also helpful. It is also prudent to recommend elevat ing the head of bed by up to 30° to prevent the recurrence of supine hypertension and decrease nocturia. CHAPTER 451 Disorders of the Autonomic Nervous System Pharmacologic agents are quite effective. Fludrocortisone is a min eralocorticoid that expands the plasma volume, in addition to having a mild α-agonist effect. The dose is 0.1–0.2 mg/d (sometimes up to 0.4 mg/d) taken usually once in the morning. Because of its long duration of effect, it is important to monitor for supine hypertension. By increasing fluid retention, it can predispose to pedal edema, a low potassium level, headaches, and occasional mood changes. For older patients who require treatment for several years or longer, it is also prudent to check their bone density intermittently. Midodrine is a direct agonist of α1-adrenoceptors. It is prudent to start at a dose of 2.5 mg 3 times daily and increase gradually up to 15 mg 3 times daily. Most patients respond to 7.5–10 mg TID. The drug's onset of action is between 30 and 60 min, and its effect lasts up to 4 h. A usual schedule is to take it before getting out of bed, before lunch, and in mid-to-late afternoon, with the last dose usually before 6:00 p.m. to avoid nocturia and supine hypertension. Side effects include scalp tingling and goosebumps because of its stimulatory effect on pilomo tor nerve fibers and urinary urgency because of its stimulatory effect at the bladder neck. Pyridostigmine, a drug commonly used in myasthenia gravis, acts as a cholinesterase inhibitor and increases ganglionic transmission. Patients may be sensitive to the drug, so it is practical to start with 30 mg TID and increase gradually to 60 mg TID. It potentiates the effect of midodrine. It may cause abdominal cramps and diarrhea in susceptible patients. It is particularly beneficial for autonomic patients with OH and slow gastrointestinal motility. It does not promote supine hypertension, an advantage for this drug. Atomoxetine is a norepinephrine reuptake inhibitor that is useful as an adjuvant therapy. Most patients benefit from 18 mg in the morn ing. While some patients may need it midday to early afternoon, it is important to monitor for symptoms and signs of CNS stimulation such as anxiety and tremor. Droxidopa is the newest agent approved for treatment of NOH. It is a norepinephrine precursor. Treatment should start with 100 mg TID and be gradually increased to 400–600 mg TID. The medication improved orthostatic symptoms and decreased falls in PD patients. Supine hypertension remains an issue in most patients.

Desmopressin increases water reabsorption and reduces urination. Low-dose oral administration or nasal spray can be useful in reducing the frequency of nocturia that often interrupts sleep. Patients should be monitored for hyponatremia.

When patients with OH or NOH develop supine hypertension, it is important to revise their medications, monitor end-organ function, ensure elevation of the head of bed during sleep (30–45°), and use short-acting blood pressure–lowering drugs at bedtime. ■ ■POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME POTS is a common syndrome of chronic (>3 months) OI without sustained OH, accompanied by an increase in HR of ≥30 beats/min in adults (≥40 beats/min if under the age of 19 years) or an orthostatic HR >120 beats/min within 10 min of standing that subsides on sit ting or lying down. The symptoms reflect a combination of cerebral hypoperfusion (lightheadedness, blurred vision, cognitive decline, and brain fog) and sympathetic activation (palpitations, chest pain, and tremulousness). Near-syncope is common, but complete syncope is less frequent. The condition is four to five times more common in women, and most develop the syndrome between the ages of 15 and 45 years. Symptoms may flare up around menstrual cycles. PART 13 Neurologic Disorders POTS is often multifactorial, as the pathophysiology is heteroge neous: distal sympathetic denervation in the feet and legs with pre served cardiovascular sympathetic function (so-called neuropathic POTS), venous pooling, reduced cardiac function due to decondition ing, hypovolemia, altered baroreceptor regulation, increased sympa thetic activity, and rarely reduced parasympathetic activity may play a role. About half the cases follow a viral illness. Most prominent among these are Epstein-Barr virus, coronavirus, and enteroviral illnesses. The condition has increased since the COVID-19 pandemic; it is the leading manifestation of long COVID. Other POTS triggers include surgery, the postpartum period, puberty, pregnancy, concussion, and chronic emotional distress. Ehlers-Danlos syndrome is a significant predisposing condition, present in up to 25% of patients. When symp toms of POTS are prominent, patients become sedentary, exacerbating their deconditioning and leading to a vicious cycle with prolongation of the syndrome. In the chronic state, cardiovascular deconditioning becomes the common pathway. POTS comorbidities include migraine and various headache dis orders, symptoms of gastrointestinal dysmotility, chronic fatigue, fibromyalgia, gastrointestinal and bladder visceral pain, and sleep disturbances. Some patients report temperature intolerance, more to heat than cold, with impaired sweating (either increased or decreased). Patients often appear anxious in the clinic and have a tendency to be hypervigilant with respect to somatic symptoms, but the incidence of significant psychiatric disorders does not differ from that in the general population. Some patients report a new onset of various allergic symp toms (flushing, hives, and environmental and food allergies) suggestive of some type of mast cell activation syndrome. While there is no standardized approach to the diagnosis, it is important to rule out primary cardiac causes, including arrhythmias (POTS is a sinus rhythm disorder), as well as endocrine conditions that lead to sympathetic activation, such as pheochromocytoma and hyperthyroidism. In addition to routine complete blood count and electrolyte panel, it is important also to measure ferritin and vitamin D levels and correct these if low, as this helps the condition respond better to other treatments. Management has some similarities to the management of OH. Typically, it encourages the expansion of fluid volume with water (8–10 cups daily) and salt (6–8 g/d). Elastic stockings, waist high with 20–30 mmHg counterpressure, reduce venous pooling and improve venous return. Pharmacotherapy with low-dose fludrocortisone can be helpful. When symptoms of sympathetic overactivity are prominent, low doses of a beta blocker, increased gradually, can be helpful. These patients can be sensitive to beta blockers, so it is important to measure their blood pressure while on treatment; if it decreases, they would need a higher dose of fludrocortisone or the addition of a vasoactive drug such as midodrine. The latter is particularly useful in patients

with neuropathic POTS, as it counteracts the significant peripheral vasodilation that is present. In patients with gastrointestinal hypomo tility, low-dose pyridostigmine can be helpful and may improve the patient's fatigue as well. When tachycardia proves refractory to the above measures, low-dose ivabradine can also be tried. A graduated program of exercise to improve cardiac deconditioning is essential and often needs at least 6 months before significant benefit is obtained. Because of the orthostatic nature of the condition, exercise is better tolerated in the supine or sitting position (recumbent bike, rowing, swimming) and should involve a combination of aerobic cardiovascu lar training and resistance training primarily to the leg muscles. If the patient's symptoms and tolerance improve after 3 months, exercise in the upright position (treadmill, elliptical) can be gradually advanced. ■ ■SYNUCLEINOPATHIES This group of disorders is secondary to the accumulation of phos phorylated α-synuclein in various parts of the ANS. They include mul tiple system atrophy (MSA), Parkinson's disease (PD; Chap. 446) with autonomic failure, Dementia with Lewy bodies (DLB; Chap. 445), and primary autonomic failure (PAF). Pathologically, there are aggregates of misfolded α-synuclein in the CNS and PNS. Cardiovascular auto nomic denervation is more common in PD and PAF, whereas it tends to occur later in MSA and DLB. PAF is a sporadic peripheral autonomic degenerative disease that has clinical manifestations similar to those in other autonomic neu ropathies, such as diabetic autonomic neuropathy, and the autoim mune autonomic neuropathies. NOH is the prominent clinical feature and frequently associated with supine hypertension. After 5–10 years, a significant number of PAF patients develop a CNS synucleinopathy, particularly PD or DLB but also MSA. In addition to the presence of autonomic dysfunction, skin punch biopsy with immunohistochem istry staining can demonstrate small nerve fibers and intraneural α-synuclein deposition. MSA, or Shy-Drager syndrome, is a disorder that combines auto nomic failure and either parkinsonism (MSA-P) or a cerebellar syn drome (MSA-C). MSA is uncommon, with a prevalence estimated at 2–5 per 100,000 individuals. Onset is typically in the mid-fifties, men are slightly more affected than women, and most cases are sporadic. MSA generally progresses relentlessly to death 7–10 years after onset, but some patients may survive beyond 10 years. MSA-C is more com mon in Asian population, particularly in Japan, while MSA-P is the more common form in the rest of the world, including Western coun tries. A characteristic of the extrapyramidal parkinsonian phenotype is the relatively poor response to levodopa; when a response occurs, it tends to be transient. Rigidity dominates, while rest tremor is not prominent. Other distinguishing features that favor MSA-P over idio pathic PD is the early impairment of urinary control in both genders, early erectile dysfunction in men, symptomatic OH within 2 years of onset, preserved olfaction, and a lower frequency of gastrointestinal symptomatology, especially colonic hypomotility and constipation. Early autonomic dysfunction, early bladder dysfunction, female gen der, and rapid progression of disability imply a worse prognosis. Brain magnetic resonance imaging (MRI) can show iron deposition in the striatum in MSA-P, and cerebellar atrophy with a characteristic T2 hyperintense signal ("hot cross bun" sign) in the pons in MSA-C (Fig. 451-6). However, the typical MRI findings may be present only with advanced disease. Cardiac postganglionic adrenergic innervation, measured by the uptake of meta-iodobenzylguanidine (MIBG) on a radionuclear scan or fluorodopamine on positron emission tomogra phy, is usually intact in MSA, whereas it is low in the dysautonomias of PD, LBD, and PAF. The neuropathology of MSA shows neuronal loss and gliosis in many CNS regions, including the brainstem, cerebellum, striatum, and intermediolateral cell column of the thoracolumbar spi nal cord. The characteristic pathologic feature is the presence of glial cytoplasmic inclusions that stain positively for α-synuclein (early Lewy bodies) primarily in oligodendrocytes, in contrast to their neuronal localization in PD or LBD. Research has shown some transfer of these cytoplasmic

inclusions from cell to cell, akin to that of a prion (Chap. 449).

FIGURE 451-6 Multiple system atrophy, cerebellar type (MSA-C). Axial T2-weighted and FLAIR (fluid-attenuated inversion recovery) magnetic resonance images at the level of the pons demonstrate a characteristic cruciform hyperintense signal in the pons, the “hot cross bun” sign. This appearance is characteristic but not pathognomonic of MSA-C, as it can also be seen in some spinocerebellar atrophies and other neurodegenerative conditions affecting the brainstem. The images additionally demonstrate atrophy of the pons, bilateral middle cerebellar peduncles, and cerebellum. (Courtesy of Dr. Nancy Fischbein, Stanford University School of Medicine.) Management is symptomatic for NOH (see earlier section on OH), sleep disorders including laryngeal stridor, and gastrointestinal and urinary dysfunction. Gastrointestinal symptoms can be managed with frequent small meals, a soft diet, stool softeners, and bulk agents. Per sistent significant gastric and colonic hypomotility requires the admin istration of the newer motility stimulation drugs, such as prucalopride, linaclotide, plecanatide, or lubiprostone. Metoclopramide stimulates gastric emptying but should be used only as a short-term measure, if at all, because it worsens parkinsonism by blocking central dopamine receptors. Domperidone, a peripheral dopamine (D2 and D3) receptor antagonist, is also effective but is not U.S. Food and Drug Adminis tration approved for use in the United States because of its potential arrhythmogenic risk. Pharmacologic management of neurogenic blad der relies usually on muscarinic blockers to reduce bladder urgency. Oxybutynin is often a first-line agent, but increasing the dose may cause other antimuscarinic side effect such as dry mouth, dry eyes, and anhidrosis. More selective blockers (tolterodine, darifenacin, or solif enacin) produced fewer systemic side effects. Mirabegron and vibegron are selective β3-adrenergic agonists that reduces detrusor overactivity and are quite effective. A potential beneficial side effect is their gentle hypertensive effect that may help with OH management but may also require adjusting doses of other OH medications to avoid significant supine hypertension. Autonomic dysfunction also occurs in DLB (Chap. 445) with the severity usually intermediate between that of MSA and PD. In multiple sclerosis (MS; Chap. 455), autonomic complications reflect the CNS location of MS lesions (more common with brainstem and spinal cord demyelination) and generally worsen with disease duration and disability but are generally less severe than with synucleinopathies. ■ ■SPINAL CORD DISORDERS Spinal cord lesions may cause focal autonomic deficits dominated by OH, bowel dysfunction, and genitourinary dysfunction, as well as temperature dysregulation secondary to anhidrosis below the level of

 the lesion. Quadriparesis predisposes to supine hypertension and OH after upward tilting. Autonomic dysreflexia is a dramatic blood pressure increase that occurs in response to irritation of the bladder, skin, or muscles. It usually follows traumatic spinal cord lesions above the T6 level, as lesions below T6 allow for compensatory splanchnic vasodila tion and a lesser likelihood of autonomic dysreflexia. The condition sometimes interferes with patient care, particularly when patients require urinary catheterization for distended bladder or rectal manage ment for constipation and fecal impaction. In addition to blood pres sure surges that may induce intracranial vasospasm or hemorrhage, other symptoms include facial flushing, headache, hypertension, pilo erection, and even cardiac arrhythmia. Sitting the patient up reduces excessive supine hypertension. Prophylactic clonidine can reduce the hypertension resulting from bladder or rectal stimulation. Disorders of the spinal cord are discussed in Chap. 453. ■ ■PERIPHERAL NERVE AND NEUROMUSCULAR TRANSMISSION DISORDERS Peripheral autonomic neuropathies are the most common cause of autonomic

insufficiency. These complex disorders can impact cardio vascular, gastrointestinal, urogenital, and sudomotor systems. They affect small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves and commonly occur in diabetes mel litus, amyloidosis, chronic alcoholism, porphyria, idiopathic smallfiber polyneuropathy, and Guillain-Barré syndrome. Neuromuscular junction disorders with autonomic involvement include botulism and Lambert-Eaton myasthenic syndrome (Chaps. 457–459). Diabetes Mellitus Diabetes mellitus remains one of the leading causes of peripheral autonomic neuropathy. The presence of autonomic neuropathy increases the mortality rate of diabetes up to threefold, even after adjusting for other cardiovascular risk factors. The neuropathy risk correlates with the product of the patient's hemoglobin A1c values and the duration of the diabetes. Early autonomic impairment is most often

manifest as cardiovascular parasympathetic hypofunction. As diabetes progresses, sympathetic hypofunction follows, dominated by OH. The autonomic involvement also predicts other complications including cor onary artery disease, renal disease, stroke, and sleep apnea. It also plays a significant role in the gastrointestinal dysmotility, which may further complicate glycemic control. Improved glycemic control significantly reduces the long-term risk of autonomic cardiovascular neuropathy. Diabetes mellitus is discussed in Chaps. 415–417.

Amyloidosis Amyloidosis, both acquired primary (AL) and hered itary transthyretin (hATTR) types, leads to autonomic neuropathy. Patients usually present with a distal sensorimotor polyneuropathy accompanied by autonomic insufficiency, but an autonomic neuropa thy in isolation may also occur. A history of carpal tunnel syndrome is common. Postmortem studies reveal amyloid deposition in many organs, including two sites that contribute to autonomic failure: intra neural blood vessels and autonomic ganglia. For AL amyloidosis, the diagnosis is made by blood tests showing monoclonal gammopathy and elevated free light chains (with lambda more often than kappa being the culprit). For hATTR, If genetic testing for TTR mutations is negative, confirmation usually requires histologic diagnosis (abdomi nal fat pad, rectal mucosa, nerve/muscle biopsy, or myocardial biopsy in cases with cardiomyopathy) to search for amyloid deposits. Genebased treatments (either RNA silencing or antisense oligonucleotides) are effective for hATTR amyloidosis. Treatment for AL amyloidosis usually relies on chemotherapeutic drugs. Death is usually due to cardiac or renal involvement. Amyloidosis is discussed in Chap. 117. PART 13 Neurologic Disorders Alcoholic Neuropathy Abnormalities in parasympathetic vagal and efferent sympathetic function are usually mild in alcoholic poly neuropathy. OH is usually due to brainstem involvement, rather than injury to the PNS. Impotence is a common symptom, but concurrent gonadal hormone abnormalities may play a role in this symptom. Clinical symptoms of autonomic failure generally appear only when the stocking-glove polyneuropathy is severe, and there may be coex isting ataxia or Wernicke's encephalopathy (Chap. 318). Autonomic involvement may contribute to the high mortality rates associated with alcoholism. Alcohol use disorders are discussed in Chap. 464. Porphyria Autonomic dysfunction occurs only in the hepatic por phyrias. It is documented in acute intermittent porphyria, but may also occur with variegate porphyria and hereditary coproporphyria. Sym pathetic overactivity dominates the clinical presentation. Autonomic symptoms include tachycardia, sweating, urinary retention, abdomi nal pain, nausea and vomiting, insomnia, hypertension, and (less commonly) hypotension. Often, patients have psychiatric symptoms dominated by anxiety, but depression and bipolar-like presentations may occur. Abnormal autonomic function can occur both during acute attacks and during remissions. Elevated catecholamine levels during acute attacks correlate with the degree of tachycardia and

hypertension that is present. Porphyria is discussed in Chap. 428. Guillain-Barré Syndrome (GBS) GBS often causes autonomic instability, more often but not exclusively in more severe cases. Car diovascular dysautonomia can be life-threatening, and gastrointestinal autonomic involvement, abnormal sweating, and pupillary dysfunction may also occur. The dysautonomia is secondary to the demyelination of the vagus and glossopharyngeal nerves and the preganglionic sympathetic white rami communicantes. In some cases, autonomic involvement outweighs other manifestations of the motor or sensory neuropathy. Acute autonomic and sensory neuropathy is a variant that spares the motor system and presents with NOH and varying degrees of sensory loss. The treatment is similar to that for GBS (IV immuno globulin or plasma exchange), but the prognosis is less favorable, with persistent sensory deficits and variable degrees of OH present in many patients. GBS is discussed in Chap. 458. Autoimmune Autonomic Ganglionopathy (AAG) AAG is a rare form of dysautonomia. Approximately 100 Americans are diag nosed each year. It affects people of both sexes and all ages, although it is more common in women and in adults. Other names for this

condition are acute pandysautonomia, idiopathic subacute autonomic neuropathy, and autoimmune autonomic neuropathy. It is typically associated with high titers of autoantibodies against the α3 subunit of the ganglionic acetylcholine nicotinic receptor (g-AChR α3). AAG often follows a triggering event: infection, surgery, autoimmunity, or malignancy in most patients. This condition is important to recognize because it is a treatable disorder. Symptoms mimic those caused by ganglion-blocking drugs without neuromuscular block, depending upon on which ANS division predominates. Ocular involvement leads to mydriasis and cycloplegia with blurred vision. Bronchial involve ment leads to bronchodilation. Gastrointestinal involvement leads to reduced motility and secretion. Genitourinary involvement leads to urinary retention and impaired erection and ejaculation. Cardiac involvement leads to mild tachycardia. Vascular involvement reduces sympathetic tone and produces postural hypotension. Involvement of salivary and sweat glands leads to dry mouth and impaired sweat ing. Symptoms of autonomic failure occur in various combinations: syncope and OH; labile blood pressure; gastrointestinal hypomotility; bladder hypomotility; pupillary dysfunction with Adie’s tonic pupil (slow reaction to light, bitter reaction to accommodation, slow relax ation afterward); dry mouth and eyes; and anhidrosis. Optic neuritis has also been reported in smokers with positive g-AChR α3 antibodies. Some patients with higher titers of AAG have a paraneoplastic form of the disease associated with small cell lung carcinoma, thy moma, or lymphoma (Chap. 99). Therefore, it is prudent to search for malignancy in the initial workup of AAG. Although no large studies have evaluated the efficacy of various treatments in AAG, IV immu noglobulin or plasmapheresis is generally used as first-line therapy, with glucocorticoids, rituximab, or mycophenolate mofetil, alone or in combination, used for nonresponders. Symptomatic treatment is of utmost importance, with attention to OI, gastrointestinal dysmotility, and genitourinary disturbances. Nonpharmacologic treatments such as exercise, increasing salt and fluid intake, compression stockings, and good sleep habits can also help. Seronegative Autoimmune Autonomic Neuropathy (SAAN) SAAN is likely a seronegative variant of AAG, as this con dition presents with subacute autonomic disturbances similar to AAG. Pathology shows preferential involvement of small unmyelinated nerve fibers, with sparing of larger myelinated ones. The neuropathy follows a viral infection in about half of cases. Several cases have been associ ated with use of checkpoint inhibitors. About one-third of untreated patients improve over time. Management is similar to that for AAG, although some patients may respond better to glucocorticoids as firstline therapy. Botulism Botulinum toxin binds presynaptically to cholinergic nerve terminals and blocks ACh release. This condition presents with

motor paralysis and signs of cholinergic failure that include blurred vision, sluggishly reactive pupils, dry mouth, dry skin, reduced gastric and colonic motility, and urinary retention (Chap. 138). Chronic Idiopathic Anhidrosis Chronic idiopathic anhidrosis is a rare condition in which patients present with heat intolerance but preserved vasomotor function. There is no associated somatic neuropathy. Some patients may have Adie’s tonic pupils as well (Ross syndrome). Acknowledgment Richard J. Barohn and John W. Engstrom contributed to this chapter in the prior edition and material from that chapter has been retained here. ■ ■FURTHER READING Campbell WW, Baron RJ: The autonomic nervous system, in DeJong’s The Neurologic Examination, 8th ed. WW Campbell, RJ Barohn (eds). Philadelphia, Wolters Kluwer, 2020. Cheshire WP: Autonomic history, examination and laboratory evalu ation. Continuum (Minneap Minn) 26:25, 2020. Donadio V et al: Phosphorylated α-synuclein in skin Schwann cells: A new biomarker for multiple system atrophy. Brain 146:1065, 2023.

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