c00324 # 154 Disorders of the Autonomic Nervous System: Autonomic Dysfunction in Pediatric Practice

Jose-Alberto Palma, Lucy Norcliffe-Kaufmann, Cristina Fuente-Mora, Leila Percival, Christy Spalink, and Horacio Kaufmann

s0010 ## INTRODUCTION

p0010 Dysfunction of the autonomic nervous system (ANS) is an increasingly recognized health problem in the pediatric population. Patients with ANS dysfunction may present with a number of seemingly unrelated symptoms, including lightheadedness on standing, syncope, labile blood pressure, problems with sweating or thermoregulation, gastrointestinal dysmotility, bladder urgency or incontinence, and sleep abnormalities.

p0015 In clinical practice, the vast majority of complaints in children referred to an autonomic disorders clinic correspond to physiologic responses to emotional states. Neuronal pathways connect the limbic system to the autonomic system, and as a consequence, emotions have a profound effect on autonomic outflow to the organs.[1] For instance, anxiety or panic in children can manifest as tachycardia, hypertension, diaphoresis, mydriasis, dyspnea, orthostatic intolerance, nausea, diarrhea, and insomnia. In these cases, rather than a primary autonomic disorder, the symptoms result from activation of the classic "flight-or-fight" autonomic response to a perceived (but not always obvious) threat.

p0020 The most common reason for referring children to an autonomic disorders clinic is orthostatic intolerance (i.e., dizziness, lightheadedness, or feeling about to faint when standing that resolves when sitting or supine). The vast majority of these children have no structural abnormalities of the ANS, but functional benign disorders. The two most common functional autonomic disorders in children are transient loss of consciousness due to reflex (vasovagal) syncope and orthostatic intolerance related to the postural tachycardia syndrome (PoTS). Emotions can play a powerful role in both disorders.

p0025 Autonomic dysfunction in children can be secondary to metabolic disorders, including obesity, anorexia, and diabetes. Severe, sometimes life-threatening derangements of autonomic function occur in a number of rare genetic and autoimmune disorders. Autonomic dysreflexia as a result of spinal cord lesions and afferent baroreflex failure as a result of neck tumors or as sequelae of surgery or radiotherapy can occur in children and adolescents and presents with dramatic blood pressure volatility.

p0030 The diagnostic workup of a child with suspected autonomic dysfunction should focus on defining whether the condition is transient or chronic and whether autonomic outflow to the organs is exaggerated or impaired. Evaluation of the ANS in children should be performed in a dedicated clinical laboratory, and results need to be interpreted against age-matched normative values. Once the underlying cause is established, autonomic symptoms can be successfully treated most of the time.

s0015 ## ANATOMY AND PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

s0020 ### Embryologic Development

p0035 Sympathetic and parasympathetic neurons and epinephrine-producing adrenal cells arise from *neural crest cells* in the ectoderm, one of the three primary embryonic germ layers (the other two being mesoderm and endoderm). The sympathetic ganglia form from neural crest cells that migrate to the dorsal aorta and express the enzymes of the catecholamine pathways to produce norepinephrine. Sympathetic neurons are dependent on nerve growth factor.

p0040 Parasympathetic ganglia innervating the head, heart, and respiratory tract and postganglionic parasympathetic neurons innervating the pelvic organs also derive from neural crest cells. Vagal and sacral neural crest cells proliferate and differentiate to form the enteric nervous system, a complex neuronal network that controls motility, secretion, and blood supply along the gastrointestinal tract.

p0045 Knowledge of embryologic development of the ANS is useful to understand several hereditary sensory and autonomic neuropathies (HSANs) because the pattern of neuronal loss and autonomic phenotype depends on which stage in development is interrupted.

Anatomy of the Autonomic Nervous System

s0025

p0050 The ANS innervates most of the organs in the body and controls involuntary functions to maintain homeostasis. In 1898, physiologist John Langley divided the ANS into three branches: sympathetic, parasympathetic, and enteric.[2] The sympathetic and the parasympathetic nervous system have opposing actions. The sympathetic system predominates during fight-or-flight situations, in which the presence of a perceived threat (either physical or mental) leads to the release of epinephrine and norepinephrine, which increase heart rate, blood pressure, and sweating, and promotes urinary and fecal retention. This is also the case during physical exercise. Conversely, the parasympathetic system predominates during resting conditions, lowering the heart rate and blood pressure and promoting digestion to conserve and store energy (e.g., during hibernation in certain animals).

Efferent Autonomic Pathways

s0030

p0055 The autonomic outflow from the central nervous system (CNS) to the effector organs consists of a two-neuron pathway with one synapse in the peripheral autonomic ganglia (Figure 154-1).

s0035 **Sympathetic Efferent Pathways.** The cell bodies of preganglionic *sympathetic neurons* are in the intermediolateral cell column (IML) of the thoracic and lumbar spinal cord (levels T1 through L3). Preganglionic sympathetic axons leave the spinal cord as small myelinated fibers to synapse with (post) ganglionic neurons in sympathetic ganglia close to the spinal cord. Unmyelinated axons from postganglionic neurons emerge from sympathetic ganglia to synapse with target organs.

p0060

p0065 Preganglionic sympathetic neurons in the IML cell column receive direct descending excitatory inputs from hypothalamic nuclei and from the ventromedial and rostral ventrolateral medulla (RVLM). Preganglionic sympathetic axons exit the spinal cord through the ventral roots toward paravertebral or prevertebral ganglia.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

f0010

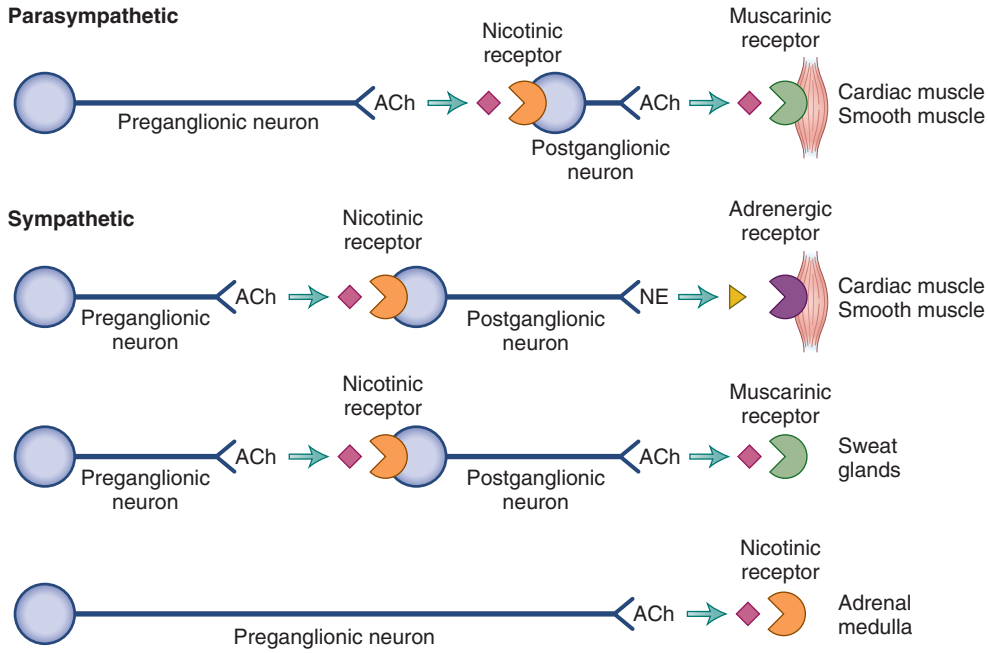


Figure 154-1. Elements of the parasympathetic and sympathetic nervous systems. Most organs receive both sympathetic and parasympathetic innervation, except for the blood vessels (only sympathetic adrenergic), the sweat glands (only sympathetic cholinergic), and the adrenal medulla (receives direct sympathetic innervation from the intermediolateral cell column in the spinal cord).

p0070 At the paravertebral ganglia (located at the sides of the spinal cord), preganglionic fibers may synapse on a postganglionic neuron at the same level or branch and run rostrally or caudally to synapse on a large number of postganglionic neurons at different levels.

p0075 Preganglionic fibers also pass through the paravertebral ganglia without synapsing to form the splanchnic nerves that innervate the prevertebral ganglia (located anterior to the spinal cord) or the adrenal medulla.

p0080 Paravertebral ganglia provide long unmyelinated axons to all sympathetically innervated tissues and organs except those in the abdomen, pelvis, and perineum. Postganglionic sympathetic fibers join the peripheral somatic nerves via the gray rami communicantes, and thus their distribution is similar to that of the corresponding somatic nerve. Sympathetic fibers in somatic nerves provide vasomotor, sudomotor, and pilomotor innervation to the extremities and trunk.

p0085 The lower cervical and upper thoracic ganglia innervate the heart via the cardiac plexus and the tracheobronchial tree via the pulmonary plexus. Prevertebral ganglia innervate the abdominal, pelvic, and perineal organs. Preganglionic fibers from the T5 to T12 levels are carried by the thoracic splanchnic nerves and form the celiac plexus, which innervates all abdominal viscera except the descending colon. Sympathetic nerves inhibit muscle contractility of the bladder and bowel, allowing storage of urine and feces. These are also involved in ejaculation.

s0040 p0090 **Parasympathetic Efferent Pathways.** The cell bodies of preganglionic *parasympathetic neurons* are located in the brainstem and at the sacral (S2-S4) level of the spinal cord. Axons of preganglionic parasympathetic neurons are myelinated and leave the brainstem or spinal cord to synapse with cell bodies of postganglionic parasympathetic neurons in autonomic ganglia close to (or within) the effector organs. Short unmyelinated postganglionic parasympathetic fibers synapse with target tissues.

p0095 Cell bodies of cranial parasympathetic (preganglionic) neurons are located in the midbrain, pons, and medulla. Efferent axons from these neurons travel in cranial nerves III, VII, IX, and X (vagus). The vagal preganglionic neurons that control respiratory and abdominal viscera are located in the dorsal motor nucleus; those that innervate the heart are in the nucleus ambiguus. Main effects of the vagus are cardioinhibitory, visceromotor, and secretomotor. Sacral preganglionic parasympathetic neurons are located in the IML cell column at the S2 to S4 levels of the spinal cord. Their axons form the hypogastric (pelvic) plexus. The sacral parasympathetic system is critical for defecation, micturition, and erection.

s0045 p0100 **Efferent Neurotransmission.** Acetylcholine is the neurotransmitter of preganglionic neurons, both sympathetic and parasympathetic. Acetylcholine, via activation of nicotinic receptors, produces excitation of postganglionic neurons. The main neurotransmitter of postganglionic sympathetic neurons is norepinephrine, which activates alpha- and beta-adrenergic receptors. The sympathetic neurons innervating sweat glands release acetylcholine, which activates muscarinic receptors. The main neurotransmitter of postganglionic parasympathetic neurons is also acetylcholine, which acts on different types of muscarinic receptors (Figure 154-1).

p0105 Alpha-adrenergic receptors mediate sympathetically induced pupillary dilatation, vasoconstriction, and contraction of the vas deferens and bladder and rectal internal sphincters. Beta-receptors mediate sympathetically induced cardiac stimulation, vasodilatation, bronchodilatation, relaxation of the bladder, and endocrine-metabolic effects. Muscarinic receptors mediate pupil constriction, salivary and lacrimal secretion, cardiac inhibition, bronchoconstriction, stimulation of the motility and secretion of the gastrointestinal tract, evacuation of bladder and rectum, and erection.

Afferent Autonomic Pathways s0050

p0110 The classic descriptions of the ANS were of a purely efferent motor system. The ANS, however, has afferent pathways that run parallel to the efferent pathways and can also be divided into sympathetic and parasympathetic.

p0115 *Parasympathetic* afferents are small-diameter fibers that transmit information to the CNS via the vagus (X) and

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

glossopharyngeal (IX) nerves and have their cell bodies in the nodose and petrosal ganglia, respectively. Vagal afferents relay information from aortic, cardiac, pulmonary, and gastrointestinal receptors. Glossopharyngeal afferents carry signals from baro- and chemoreceptors in the carotid sinus. Parasympathetic afferents synapse with neurons in the medullary nucleus of the solitary tract in the brainstem, which is the main central relay station for incoming autonomic information.

p0120 *Sympathetic* afferents are a network of small-diameter sensory fibers that relay information about an array of physiologic variables, including the mechanical, thermal, chemical, metabolic, and hormonal status of the skin, muscle, joints, teeth, and viscera. They are responsible for muscular and visceral sensations, vasomotor activity, hunger, thirst, and "air hunger." These neurons synapse with neurons in lamina I of the dorsal horn of the spinal cord. Lamina I neurons in turn project densely to the IML cell column synapsing with preganglionic sympathetic neurons, thus forming a spino-spinal loop for autonomic reflexes.

s0055 Central Nervous System Integration

p0125 Spinal, brainstem, and rostral cortical areas modulate signals from the afferent pathways, resulting in precise reflex activation or inhibition of autonomic efferent nerves.

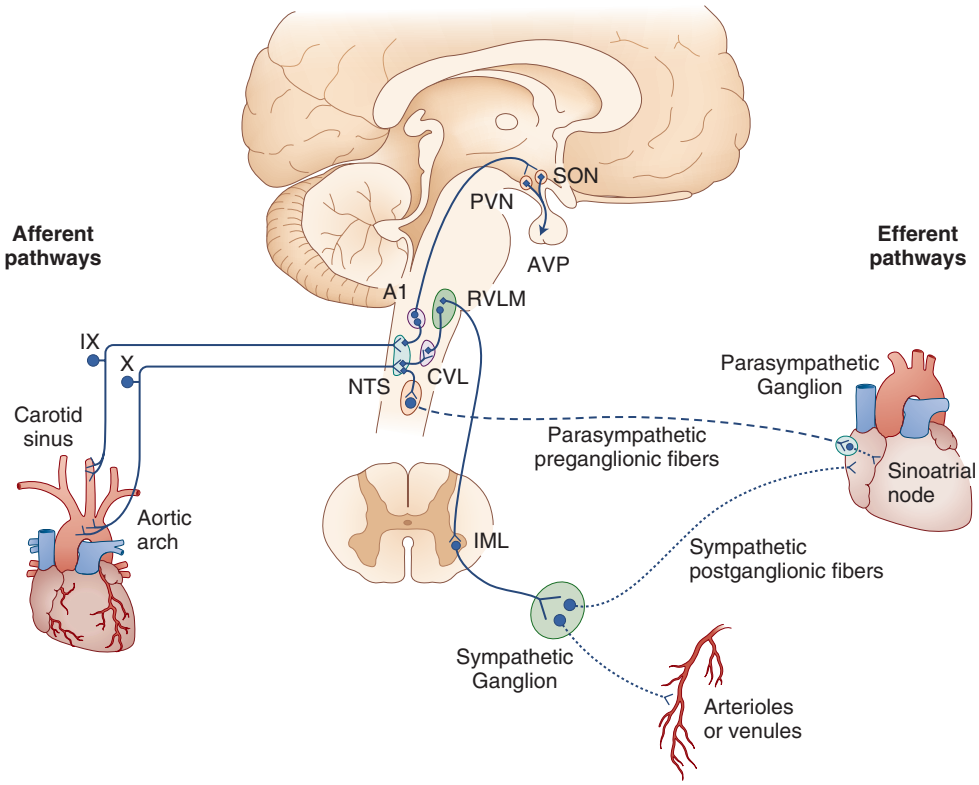
p0130 A well-studied example of an autonomic reflex pathway is the arterial baroreflex (Figure 154-2), a rapidly responding negative-feedback mechanism that buffers moment-to-moment fluctuations in blood pressure. Baroreceptors are small sensory nerve endings located in the walls of the carotid sinus and the aortic arch that respond to vascular stretch and relay information to the nucleus of the tractus solitarius (NTS) in the medulla via afferents in cranial nerves IX and X (glossopharyngeal and vagus). Baroreceptor afferent nerves are tonically active, constantly sensing distension of the blood vessels. A decrease in venous return and blood pressure when standing quickly "unloads" the baroreceptors and reduces nerve traffic to the NTS. Rapidly, projections from the NTS inhibit nucleus ambiguous (NA) neurons, reducing parasympathetic input to the sinus node, which quickens heart rate. At the same time, projections from the NTS to the caudal and then RVLM result in an increase in sympathetic efferent outflow. Baroreflex unloading also stimulates the release of vasopressin, the antidiuretic hormone, from the supraoptic and paraventricular hypothalamic nuclei. The net result of the fall in blood pressure is vasoconstriction, tachycardia, and antidiuresis, which restores blood pressure in the face of diminished venous return.

p0135 As with other polysynaptic autonomic reflexes, baroreflex information is integrated with other sensory information and with input from more rostral cortical areas.

CLINICAL APPROACH TO THE DIAGNOSIS OF PEDIATRIC AUTONOMIC DISORDERS s0060

Clinical History Taking s0065

p0140 Children with autonomic dysfunction can present with a variety of symptoms involving different organs. Obtaining a



f0015

Figure 154-2. The arterial baroreflex. The arterial baroreceptors are mechanoreceptors located in the carotid sinus (innervated by the glossopharyngeal nerve, IX) and aortic arch (innervated by the vagus nerve, X) that respond to stretch elicited by increase in arterial pressure. Baroreceptor afferents provide monosynaptic excitatory inputs to the nucleus of the solitary tract (NTS) in the brainstem. Barosensitive NTS neurons initiate a sympathoinhibitory pathway that involves projections from the NTS to the caudal ventrolateral medulla (CVL) that send inhibitory projections to sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM). There is also direct input from the NTS to the vagal preganglionic neurons of the nucleus ambiguus (NAmb). These neurons project to the cardiac ganglion neurons that promote bradycardia. The baroreflex, via the NTS, also inhibits secretion of vasopressin by neurons of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus, by inhibiting cells of the A1 noradrenergic group.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

detailed history is of paramount importance to establish a diagnosis. A structured clinical interview can provide valuable diagnostic clues. Careful review of current medications can rule out drug-induced causes. A thorough family history can disclose overlooked symptoms, which can be key to the diagnosis of genetic disorders. Emotional factors can contribute to reflex (vasovagal) syncope, PoTS, and hyperhidrosis. Although eyewitness reports are helpful, it is still essential to also listen closely to the child's interpretation of his or her symptoms. Questions should be phrased considering the child's age and developmental level. Asking open-ended questions to avoid unduly influencing a child's answers is important.

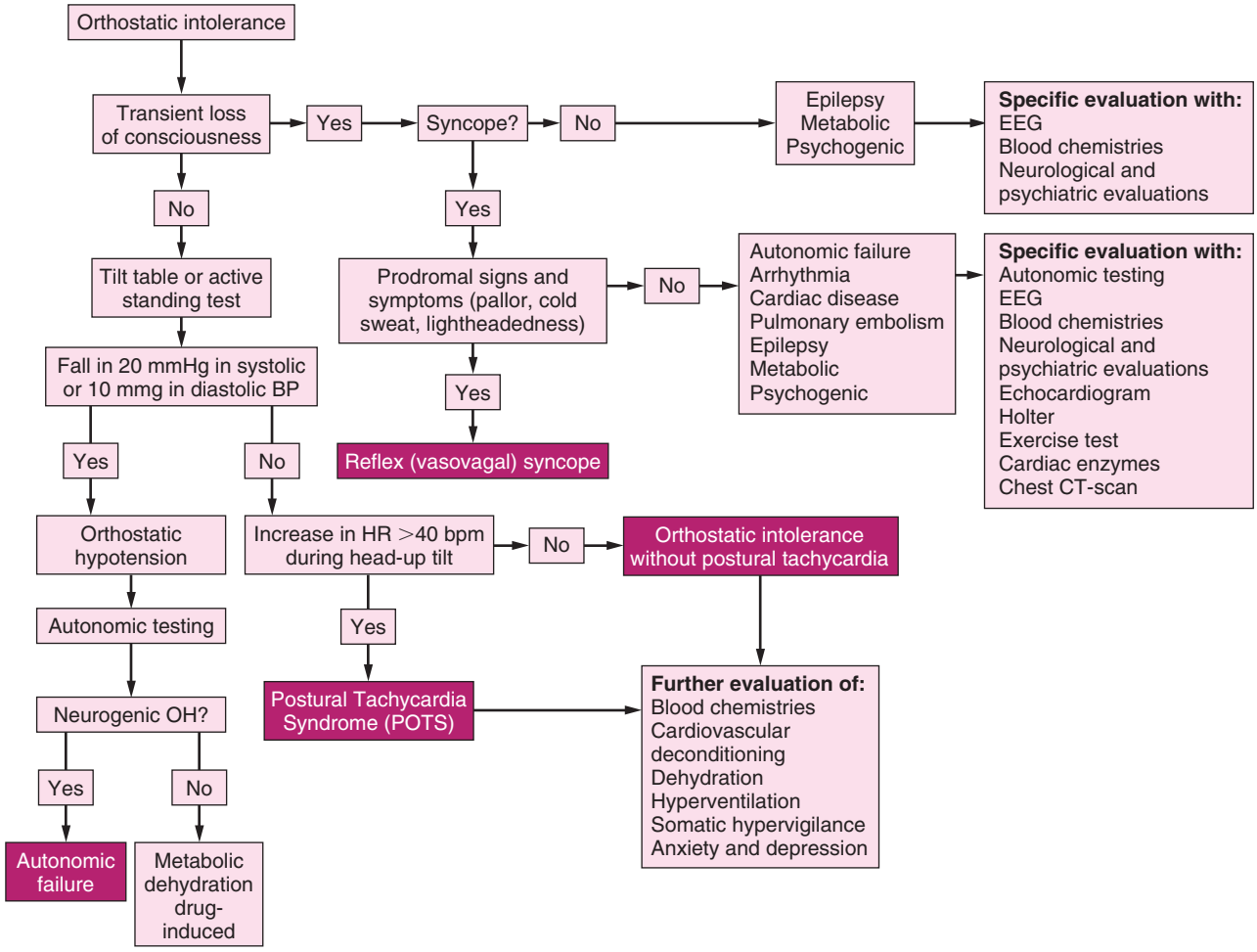
s0070 Orthostatic Intolerance

p0145 Because the sympathetic nervous system plays a crucial role in maintaining blood pressure and cerebral blood flow when standing, orthostatic intolerance with symptoms of tissue hypoperfusion is the most characteristic presentation of sympathetic failure (see following discussion). Careful inquiry about the relationship with posture and the frequency and nature of symptoms can help unravel the cause. The clinical interview should be framed with the goal of carefully reconstructing the events, signs, symptoms, and outcome of the syncopal/presyncopal episode (Figure 154-3).

s0075 p0150 **Syncope.** Most children are referred to an autonomic clinic after experiencing brief episodes of transient loss of consciousness. Although seizure is frequently suspected, syncope is a much more frequent cause. Syncope is defined as a transient loss of consciousness and postural tone resulting from global cerebral hypoperfusion; it is short-lived, with spontaneous recovery and no neurologic sequelae. The first objective is to distinguish syncope from a seizure. Urinary incontinence and myoclonic jerks can occur in children with both reflex syncope and seizures, but a clear-cut aura and postictal confusion are signs of a seizure. Tongue biting is rare in syncope but common in seizures. Syncope most commonly occurs when standing, whereas seizures have no postural predilection.

p0155 Once seizure is ruled unlikely, the clinical history should focus on distinguishing the various causes of syncope. Questions should aim to differentiate reflex (vasovagal) syncope—a reversible physiologic condition with a benign prognosis—from cardiac syncope or chronic impairment of sympathetic outflow. Although the latter is very infrequent in children, it does occur in genetic and immune-mediated autonomic disorders.

p0160 It is important to establish the circumstances preceding the event. Reflex syncope occurs in the context of gravitational stress, straining, or emotions. It is usually accompanied by prodromal symptoms; most children with reflex syncope describe dimming or blurring of vision as a result of retinal hypoperfusion and lightheadedness as a result of cerebral hypoperfusion. They may also describe feeling cold, sweating, or gastrointestinal discomfort (nausea, cramps, or the urge to defecate), all of which are signs of autonomic activation.[3] Reflex syncope is frequently preceded by hyperventilation,



f0020

Figure 154-3. Diagnostic evaluation of pediatric patients with orthostatic intolerance and transient loss of consciousness.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

which produces the paradoxical sensation of shortness of breath.[4] Eyewitness accounts may describe facial pallor and yawning. Syncope resulting from arrhythmias usually has no prodromal phase. Syncope resulting from chronic sympathetic failure is not accompanied by signs of autonomic activation such as cold sweat or nausea. Loss of consciousness with syncope lasts usually no more than 10 to 20 seconds. Identifying aggravating factors, including heat stress, dehydration, sight of blood, standing immobile for a prolonged period, and fear or anxiety, is very useful, especially when trying to educate the patient/parents on what to avoid to prevent syncope recurrence.

s0080 p0165 **Orthostatic Intolerance.** The second most commonly encountered problem in an autonomic clinic is the so-called postural tachycardia syndrome (PoTS). PoTS is a heterogenous syndrome common in young females. It is associated with a myriad of symptoms, including lightheadedness, palpitations, tremulousness, weakness, fatigue, exercise intolerance, hyperventilation, paresthesiae, shortness of breath, anxiety, chest pain, nausea, acral coldness or pain, and difficulty concentrating. Syncope is not common in PoTS. The overlap with anxiety/panic is often readily apparent.

s0085 p0170 **Abnormal Gastrointestinal Motility.** Constipation and diarrhea are common in children with functional autonomic disorders and are also a side effect of some medications or diets. Reduced salivation and a dry mouth (xerostomia) can occur in autoimmune autonomic disorders and may result in dysphagia when eating. Autonomic diseases affecting the esophagus (e.g., achalasia) may cause dysphagia and heartburn. Abdominal distension, nausea, vomiting, and early satiety as a consequence of gastroparesis can be seen in metabolic disorders (e.g., diabetes, anorexia nervosa). Neonatal severe constipation is a feature of Hirschsprung disease. Nausea and vomiting in response to emotional or physical stimuli occur in the rare genetic condition familial dysautonomia.[5]

s0090 p0175 **Urinary Symptoms.** Urinary symptoms are frequent in children, and in most cases they are not indicative of an underlying autonomic disorder. Interpretation in young children should take into account that 10% of those under 8 years of age suffer from daytime or nocturnal enuresis. Functional bladder symptoms are frequent in PoTS. In rare cases, daytime enuresis is attributable to detrusor overactivity.[6] Nocturnal enuresis is caused by either nocturnal polyuria or nocturnal detrusor overactivity.[7] Urinary retention can be seen in autoimmune autonomic disorders and in spinal cord injury. In adolescents and young men, erectile dysfunction and failure to ejaculate can be a consequence of autonomic dysfunction. Milky-colored urine may represent retrograde ejaculation.

s0095 p0180 **Thermoregulatory Abnormalities.** Anhidrosis and hypohidrosis are manifestations of sympathetic cholinergic failure, and lesions causing these abnormalities can occur anywhere from the level of the cerebral cortex to the eccrine sweat glands. Anhidrosis can lead to hyperthermia, heat stroke, and death. In spinal cord injury there often is a band of hyperhidrosis above the lesion, with anhidrosis below. Hypothermia may occur in hypothalamic disorders and spinal cord injury.

p0185 Hyperhidrosis (excessive sweating beyond that required for thermal homeostasis) can be generalized or focal. It should be distinguished from normal night sweats, which can occur in up to 12% of healthy children.[8] Patients may complain of excessive sweating, sweating of the hands and feet, or axillary sweating. In the majority of cases, the hyperhidrosis is linked to anxiety. Hyperhidrosis may accompany episodes of paroxysmal sympathetic activation in familial dysautonomia or pheochromocytoma.

s0100 p0190 **Ocular Symptoms.** Blurry vision and photophobia can be symptoms of abnormal autonomic innervation of the pupil. Impaired lacrimation may be a sign of autonomic impairment of the lacrimal glands.

s0105 p0195 **Respiratory Symptoms.** Hyperventilation is common and can be found in up to 15% of children and adolescents.[9] Hyperventilation is frequently a feature in patients with functional autonomic symptoms, including PoTS and reflex syncope.[4] Daytime symptoms of hypoventilation and central sleep apnea in children include decreased attention span, poor performance in school, and behavioral changes.

Clinical Examination and Autonomic Testing s0110

p0200 Examination of a child with suspected autonomic dysfunction should focus on ruling out accompanying sensory and motor abnormalities. Examination of pupillary responses to light can be instructive. Autonomic testing is the gold standard for diagnosis and should assess sympathetic cardiovascular, parasympathetic cardiac (cardiovagal), and sudomotor function.

Measurements of Vascular Sympathetic Function s0115

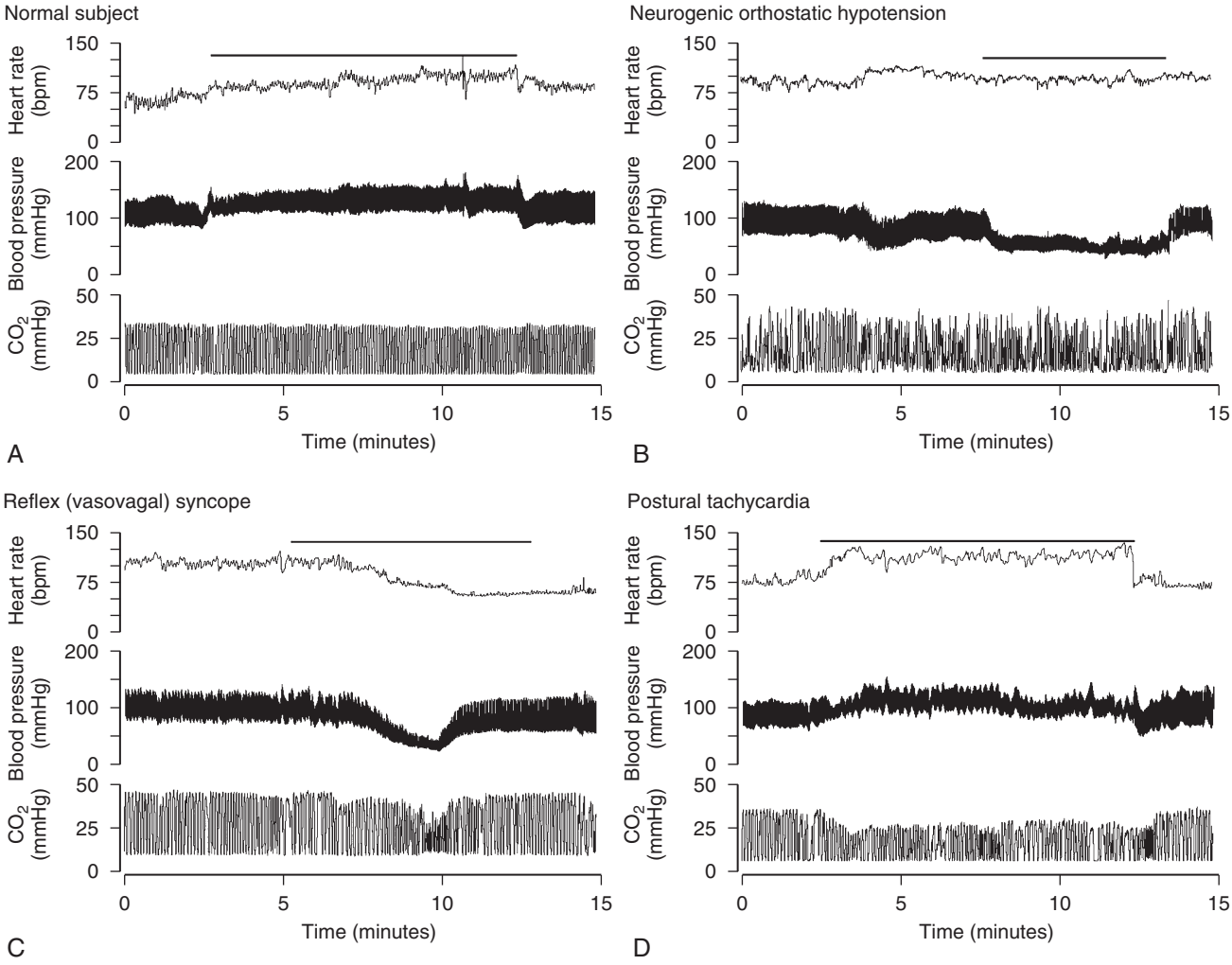
p0205 ***Orthostatic stress—active standing and passive upright tilt:*** Measurements of blood pressure and heart rate during active standing or passive upright (head-up) tilt is the most commonly used technique to assess the integrity of the sympathetic nervous system and measures the ability to withstand orthostatic (gravitational) stress. The goal is to replicate the symptoms of orthostatic intolerance in a controlled environment with continuous cardiovascular and respiratory monitoring. Excellent detailed reviews on autonomic testing are available.[10] Passive tilt with foot support prevents activation of the muscle pump and exaggerates the drop in venous return. The test involves establishing a baseline in the supine position and tilting the patient passively to an upright position (around 60 degrees) with monitoring of blood pressure and respiratory rate (RR) intervals. To provoke reflex syncope, it may be necessary to subject the patient to prolonged upright tilt (20–45 minutes) or combine tilt with lower-body negative pressure.[11] Standardized data for tilt combined with isoproterenol provocation in children is lacking and the method is controversial.

p0210 Figure 154-4 shows typical responses to a tilt table test in different autonomic disorders. In a normal child, to compensate for the gravitational pooling of blood in the upright position, sympathetic outflow to the vasculature increases, and parasympathetic outflow to the heart is withdrawn. The resulting vasoconstriction and tachycardia prevent blood pressure from falling in the upright position.

p0215 Any child with a functional ANS can be made to faint with a sufficient degree of orthostatic stress. For unclear reasons, the subset of children predisposed to suffer from recurrent reflex (vasovagal) syncope are less tolerant to gravitational stress. Initially, these children always have a normal compensatory increase in sympathetic outflow on upright tilt, with vasoconstriction, tachycardia, and maintenance of blood pressure. After a variable amount of time upright, however, sympathetic activity is abruptly withdrawn, and parasympathetic activity increases, producing a fall in blood pressure that is *always* accompanied by slowing of the heart. Heart rate may be slowed by a couple of beats or to a period of asystole.[12] In contrast, children with chronic impairment of the autonomic nerves do not have the initial normal compensatory increase in sympathetic outflow and drops in blood pressure immediately on upright tilt.

p0220 ***Valsalva maneuver:*** The Valsalva maneuver is another useful test of sympathetic function. It involves forcibly exhaling

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324



f0025

Figure 154-4. Changes in heart rate (HR), blood pressure (BP), and ventilation pattern during head-up tilt test. **A,** In a normal subject, no major changes are observed in BP, HR or end-tidal CO_2 during the tilt test. **B,** Neurogenic orthostatic hypotension features a dramatic decrease in blood pressure and absence of compensatory increase in heart rate. Hyperventilation does not occur. **C,** Reflex (vasovagal) syncope. During the episode, a dramatic decrease in blood pressure occurred, accompanied by a decrease in HR; CO_2 levels also decreased right before and during the syncope. **D,** In postural tachycardia syndrome (PoTS), heart rate increases during tilt and CO_2 levels decrease, with no significant changes in BP. The bar above the graphs denotes the period during the 60-degree-angle head-up tilt.

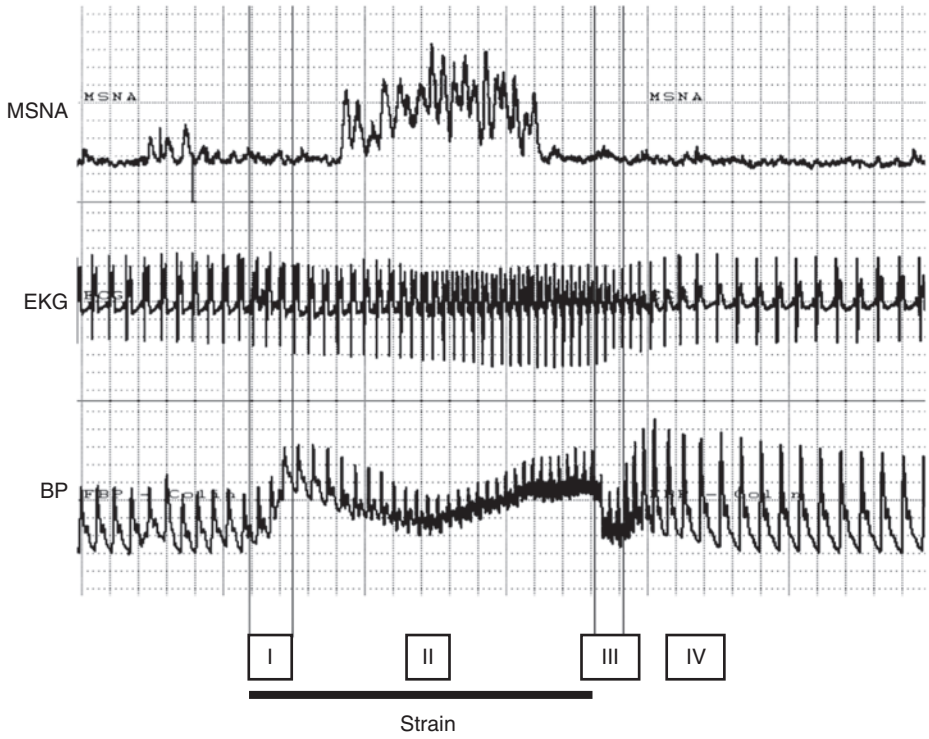
against a closed glottis to increase intrathoracic pressure acutely and reduce venous return to the heart while monitoring heart rate and beat-to-beat blood pressure. In a normal child, this stimulates a powerful reflex increase in sympathetic outflow, which prevents blood pressure from falling precipitously, and produces an overshoot in blood pressure once the strain is released (Figure 154-5). The overshoot in blood pressure is absent in children with chronic impairment of the sympathetic nerves.

p0225 ***Plasma catecholamines:*** Measurement of plasma catecholamines provides useful information on the integrity and function of sympathetic postganglionic neurons. In a normal healthy child, plasma norepinephrine levels approximately double after 10 minutes upright. The norepinephrine increase with standing is blunted in children with chronic impairment in the sympathetic nerves. Absolute levels of norepinephrine require careful interpretation in children because the upper limit of normal is much higher than in adults. Both norepinephrine and epinephrine levels are influenced by emotions, and children who are upset with the blood-draw situation may have elevated values. Therefore blood should be sampled through an indwelling catheter and only when the child is calm. In children with a suspected pheochromocytoma, metanephrines should be measured in a 24-h urine collection.

Measurements of Cardiac Parasympathetic Function s0120

In the normal resting state, heart rate fluctuates on a beat- p0230
to-beat basis because of the influence of respiratory sinus arrhythmia (RSA). In conditions where the parasympathetic innervation to the heart is impaired, these fluctuations become dampened, and heart rate variability is reduced. The most effective way to measure parasympathetic function in children is during deep paced breathing (6 breaths/min), which exaggerates RSA. The ratio of RR intervals during expiration and inspiration (E:I ratio) changes with age and is higher in children and adolescents than in elderly subjects. Careful attention should be paid to how well a child performs the breathing technique because interpretation of the E:I ratio relies heavily on test effort. The E:I ratio is reduced in disorders that affect parasympathetic efferent innervation of the heart.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324



f0030

Figure 154-5. Tracing of Valsalva maneuver in a healthy subject showing muscle sympathetic nerve activity (MSNA) recording from the peroneal nerve electrocardiogram (ECG) and beat-to-beat blood pressure measured with plethysmography in the finger (BP) showing the four characteristic phases of the maneuver. The line below the tracing denotes the strain during the maneuver. Microneurography revealed an increase in sympathetic activity during phase II that decreased during phase IV. Abnormalities in the blood pressure and heart-rate responses to the Valsalva maneuver have been described in autonomic failure where phase IV blood pressure overshoot is absent (does not occur during the first 10 seconds after removal of the strain).

s0125 Measurements of Sudomotor Sympathetic Function

p0235 Sudomotor function tests include the thermoregulatory sweat test (TST), which assesses the integrity of central and peripheral sudomotor pathways, and sudomotor axon reflex tests such as the quantitative sudomotor axon reflex test (QSART), which assesses the peripheral sympathetic cholinergic innervation of the sweat glands. Electrochemical skin conductance can be also used to estimate sweating function.

s0130 Additional Tests

p0240 Other useful tests indicated in some cases include nerve conduction studies, brain magnetic resonance imaging (MRI), gastrointestinal motility and urodynamic studies, and polysomnography. Skin biopsy with assessment of intraepidermal nerve fiber density may be useful, although results in children may be difficult to interpret. A complete blood count and a comprehensive metabolic panel are also recommended to rule out secondary causes of autonomic symptoms. Ambulatory 24-hour blood pressure monitoring while keeping a diary is extraordinarily useful to identify abnormalities in blood pressure regulation, its circadian rhythm, and aggravating factors.

s0135 PEDIATRIC AUTONOMIC DISORDERS

p0245 Pediatric autonomic disorders can be classified in several ways. Table 154-1 depicts proposed classification schemes based on the pathophysiological features of autonomic dysfunction in children. In clinical practice, the main goal is to distinguish functional disorders, which are very common, from the more severe, but rare disorders.

FUNCTIONAL DISORDERS OF UNKNOWN ORIGIN s0140

Reflex (Vasovagal) Syncope s0145

p0250 Reflex syncope (i.e., the common faint, also known as vasovagal, neurally mediated, or neurocardiogenic syncope) refers to a sudden drop in blood pressure and slowing of the heart rate causing impaired cerebral perfusion that leads to a brief episode of loss of consciousness and muscle tone.[13] Patients with reflex syncope usually describe classical prodromal signs and symptoms (pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing), and many children begin hyperventilating in the time leading up to the faint. Hyperventilation-induced hypocapnia reduces cerebral blood flow and induces vasodilatation in skeletal muscle. In some instances, these factors may be the main reason for increased susceptibility to fainting.[4] If blood pressure continues to fall, cerebral and retinal hypoperfusion (visual disturbances, concentration difficulties, and lightheadedness) develop just before the loss of consciousness.

p0255 The prevalence of reflex syncope in the pediatric population is high (Figure 154-6). A survey of young adults averaging 20 years of age showed that about 20% of males and 50% of females reported having experienced at least one syncopal episode in their lifetime.[14] The median age at the first episode of reflex syncope is ~15 years.[15]

p0260 Vasovagal syncope requires an acute reversal of the normal autonomic outflow and only occurs in children with a functional ANS.[16] Therefore the diagnosis of vasovagal syncope rules out sympathetic insufficiency resulting from an autonomic neuropathy. Rather than a medical disorder, reflex syncope is a physiologic response that occurs in otherwise

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

t0010 **TABLE 154-1** Classifications of Pediatric Autonomic Disorders

Etiology	Topography	Frequency	Neurotransmission
Functional Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia	**Generalized** Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Hereditary sensory autonomic neuropathies Other rare genetic disorders Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Immune-mediated	**Common** Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Obesity Diabetes Anorexia nervosa Other metabolic disorders	**Pandysautonomia (adrenergic and cholinergic failure)** Autoimmune autonomic ganglionopathy Acute autonomic and sensory neuropathy Guillain-Barré syndrome Paraneoplastic neuropathies Porphyria
Inherited Hereditary sensory autonomic neuropathies Other rare genetic disorders	**Pupil** Argyll Robertson pupil Adie pupil Horner syndrome Pourfour du Petit syndrome	**Rare** Immune-mediated Traumatic Hereditary sensory autonomic neuropathies Other rare genetic disorders	**Pure adrenergic failure** Dopamine-beta hydroxylase deficiency Pure adrenergic neuropathy
Metabolic Obesity Diabetes Anorexia Other metabolic disorders	**Face** Cluster headache Harlequin syndrome Gustatory sweating		**Pure cholinergic failure** Botulism Lambert-Eaton syndrome Adie pupil Chagas disease Acute cholinergic neuropathy
Immune-mediated Autoimmune autonomic ganglionopathy Guillain-Barre syndrome Anti-NMDA receptor encephalitis Paraneoplastic autonomic neuropathy Sjögren disease	**Limbs** Raynaud phenomenon Acrocyanosis Primary idiopathic hyperhidrosis		
Infectious Chagas disease HIV Tetanus			
Neoplasia Catecholamine-secreting tumors Brainstem and posterior fossa tumors			
Trauma and malformations Spinal cord injury Traumatic brain injury Syringomyelia Arnold-Chiari			
Drugs			
Postsurgical or postradiotherapy Acquired baroreflex failure			

healthy subjects under certain physiologic and emotional stimuli. Scenarios likely to provoke reflex syncope are motionless standing, elevated ambient temperatures, and dehydration. Known emotional triggers are fear, anger, blood sampling, pain, and TV programs about medical matters or animal biology.

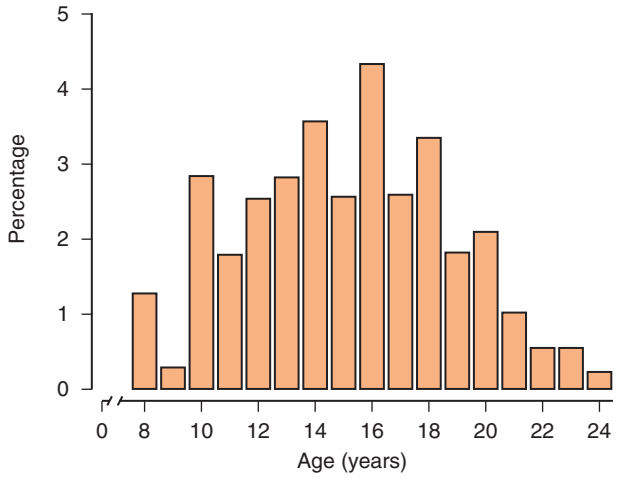
p0265 In most cases, reflex syncope can be diagnosed by eyewitness accounts and careful reconstruction of the event. In cases where the diagnosis is not straightforward, prolonged tilt testing can be helpful by replicating symptoms while recording the typical acute fall in blood pressure and slowing of the heart rate (Figure 154-4).

p0270 Key aspects of the management of young patients with reflex syncope include reassurance, advice, and patient education. Time should be taken to identify triggers that exaggerate venous pooling and provoke syncope. Children should be taught nonpharmacologic measures that can prevent or abort the episode, including slow breathing and muscle-tensing maneuvers to increase venous return. Increasing salt and water intake and sleeping with the head of the bed raised are helpful nonpharmacologic means to expand intravascular volume. In cases of refractory reflex syncope, the short-acting pressor agent midodrine can be used "on demand" to improve orthostatic intolerance before situations known to trigger syncope.[17] Pacemakers are ineffective.[18]

Postural Tachycardia Syndrome s0150

p0275 Postural tachycardia syndrome (PoTS) is a complex disorder that is not well understood. It is characterized by chronic symptoms of orthostatic intolerance accompanied by a heart-rate increment within 10 minutes of standing or head-up tilt

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324



f0035

Figure 154-6. Histogram showing the incidence of reflex (vasovagal) syncope in a population of young individuals up to the age of 24. The peak incidence is around 16 years old. *(Adapted with permission from Colman N, Nahm K, Ganzeboom KS, et al. Clin Auton Res. 2004 Oct;14 Suppl 1:9-17).*

with no orthostatic hypotension. Current consensus criteria of PoTS require, at least, a heart rate increment of 40 beats/min in children aged 12 to 19 years[13] (Figure 154-4).

p0280 Symptoms may develop gradually or acutely, range from mild to severe, and resolve spontaneously or continue intermittently for years. Syncope is not a typical feature of PoTS. However, because reflex syncope is frequent in the general population, it can also happen in subjects with PoTS.

p0285 Many children with PoTS also report symptoms not attributable to orthostatic intolerance, including those of functional gastrointestinal or bladder disorders, chronic headache, fibromyalgia, and sleep disturbances.

p0290 The pathophysiology of PoTS is unclear but likely involves a combination of factors, including cardiovascular deconditioning, hyperventilation, and volume depletion. Emotional comorbidities, including somatic hypervigilance, anxiety, and depression, are common and contribute to symptom chronicity.[19] The severity of the symptoms is often linked to the degree of hyperventilation-induced hypocapnia, which exacerbates venous pooling and tachycardia.[4] Many patients with PoTS go on to develop additional symptoms, including constipation, bloating, bladder sensitivity disorders, and chronic headache, and despite comprehensive workup, usually no structural cause can be identified.

p0295 Few patients with PoTS (5%) are seropositive for antibodies against the ganglionic acetylcholine receptor. This likely represents a false positive, as their titer values are low, and this prevalence is not different from that in healthy subjects. In a minority of cases there seems to be a mild sympathetic denervation in the lower limbs ("neuropathic" PoTS).[20] Others have increased plasma norepinephrine concentrations ("hyperadrenergic" PoTS).[19] More recently PoTS is being recognized in patients with Ehlers-Danlos syndrome, a connective tissue disorder.[19] Whether these findings are incidental, causative, or contributors to the pathophysiology is unknown. Moreover, orthostatic tachycardia of 40 bpm is a frequent finding in asymptomatic young children, so the relationship of the symptoms with the tachycardia is also unclear.[21]

p0300 Management of PoTS should begin by removing any medications that produce tachycardia, including norepinephrine reuptake inhibitors and stimulants. Surreptitious use of diuretics should be ruled out in any adolescent or young adult with elevated renin levels. Exercise training and cognitive behavioral therapy are the most appropriate inventions.[19] Correcting the standing heart rate with beta blockers or cholinesterase inhibitors may not be effective to improve symptoms.[22] Patients are particularly challenging to manage, especially when a conditioned tachycardic response to standing is combined with lack of insight and behavioral amplification.[19]

Orthostatic Intolerance without Tachycardia s0155

p0305 Orthostatic intolerance can also appear in subjects without postural tachycardia. As in PoTS, autonomic abnormalities are minimal or absent, and the wide spectrum of clinical complaints is generally disproportionate to the degree of abnormality found on testing, suggesting that both disorders share a psychological substrate. Their etiology remains incompletely understood and is likely heterogeneous, including hyperventilation and cardiovascular deconditioning.[23] Psychological factors, somatic hypervigilance, and anxiety have been reported to occur in higher frequency in these patients and likely contribute to symptom severity.[24] Treatment strategies are similar to those used in subjects with PoTS.

Metabolic Disorders s0160

Obesity s0165

p0310 The prevalence of pediatric obesity (defined as a body mass index [BMI] ≥ 95th percentile for age and sex) has more than tripled during the past decades in the United States, and around 20% of children and adolescents are now overweight. Children of African American, Hispanic, and American Indian ancestry are at particular risk. Obesity-related diseases, including obstructive sleep apnea, nonalcoholic fatty liver disease and cirrhosis, and type-2 diabetes mellitus, are increasingly diagnosed in pediatric patients.[25]

p0315 Epidemiologic studies have evaluated the effect of obesity in cardiac autonomic modulation in children. Most studies show an increase in sympathetic and a decrease in parasympathetic function[26] with abnormal cardiac circadian patterns.[27] The pathophysiology of autonomic abnormalities in obesity is not well understood but is likely mediated by comorbidities such as sleep apnea,[28] metabolic abnormalities,[29] and arterial hypertension.[30] Children with obesity as a result of genetic disorders, such as Prader-Willi syndrome, appear to have diminished parasympathetic nervous system activity.[31] Autonomic dysfunction in children can also be seen in the rare disorder rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD).[32]

Eating Disorders s0170

p0320 Anorexia nervosa is a potentially life-threatening eating disorder characterized by an intense fear of gaining weight, distorted body image, and amenorrhea. It affects 0.5% to 4% of adolescent girls in the United States, and its incidence has increased over the past few decades.[33]

p0325 Children with anorexia are predisposed to arrhythmias and sudden cardiac death. Bradycardia, hypotension, and cardiac atrophy are all features of the disease. Patients have significantly lower heart rates at night and increased heart-rate variability.[34,35] These abnormalities are reversible after weight recovery.[36] Bulimia nervosa affects 1% to 2% of adolescent girls in the United States and has similar cardiovascular autonomic findings.[37]

Diabetes Mellitus s0175

p0330 Although diabetes mellitus is one of the most common causes of autonomic dysfunction in adults, signs and symptoms of

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

autonomic dysfunction are infrequent in pediatric patients.[38] However, autonomic neuropathy should be considered in adolescents and young adults with long duration of type 1 diabetes mellitus,[39] who may have early evidence of cardiovascular autonomic dysfunction.[40,41]

s0180 Other Metabolic Disorders

p0335 Hypothyroidism (with symptoms of fatigue, dry skin, sleep disturbances, and constipation) and hyperthyroidism (with symptoms of fever, tachycardia, hypertension, and gastrointestinal abnormalities) can be considered forms of autonomic dysfunction. Symptoms of Addison disease include hypotension, hyperpigmentation, and adrenal crises.

s0185 Autonomic Dysfunction Secondary to Focal Disease

p0340 Areas distributed throughout the neuraxis, including the anterior insula, anterior cingulate cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial nucleus, and several regions of the medulla, are involved in autonomic control, particularly in cardiovascular regulation.[42] Therefore lesions of various etiologies (e.g., trauma, hydrocephalus, demyelination, stroke, malformations, tumors) can potentially cause autonomic dysfunction. Most frequently, these lesions cause paroxysmal sympathetic hyperactivity (sometimes referred to as "sympathetic storms") with hypertension and tachycardia. Abnormalities in pupillary response, sweating, and thermoregulation have been also described.[43] Syncope, sleep apnea, and cardiorespiratory arrest have been reported in association with Arnold-Chiari malformation type 1.

p0345 Spinal cord injury in the pediatric population is relatively rare.[44] More than half of pediatric spinal cord injuries occur in the cervical area. Signs and symptoms depend on the level of the lesion and whether the section is complete or incomplete, although they generally include motor and sensory deficits, bowel and bladder incontinence, and cardiovascular dysfunction. Destruction of the descending cardiovascular autonomic pathways results in (a) the blunted release of norepinephrine when upright, leading to neurogenic orthostatic hypotension, and (b) the loss of inhibitory and excitatory supraspinal input to the sympathetic preganglionic neurons, leading to unrestrained sympathetic activity of fibers arising below the level of the lesion referred to as "autonomic dysreflexia," particularly in subjects with an injury at the T6 level or above. Autonomic dysreflexia is characterized by the acute elevation of arterial blood pressure and bradycardia, although tachycardia also may occur. A variety of stimuli can trigger episodes of autonomic dysreflexia, including bladder or bowel distention, infections, and inflammation. Treatment requires the resolution of the offending insult. Antihypertensive treatment with nifedipine, nitrates, and captopril is commonly used.[45]

p0350 Syringomyelia produces partial interruption of sympathetic output pathways in the IML column. Its autonomic manifestations include Horner's syndrome, sudomotor and vasomotor dysfunction, and trophic changes in the limbs, particularly the hands.

s0190 Acquired Afferent Baroreflex Failure

p0355 Bilateral destruction of baroreceptor afferent neurons in the glossopharyngeal and vagus nerves that relay information to the NTS can result in afferent baroreflex failure.[46] Patients with baroreflex failure have extremely labile blood pressure and heart rates. Many alternate between orthostatic hypotension and paroxysmal hypertension. Hyperadrenergic signs and symptoms usually dominate the clinical picture and can resemble those of a pheochromocytoma.

p0360 Causes of afferent baroreflex failure include nerve injury secondary to neck surgery or delayed effect of radiotherapy to the neck for cancer, or trauma; brainstem strokes that damage the nucleus of the solitary tract and other areas of the brainstem; and rare hereditary conditions that affect the development of afferent baroreceptor pathways, including familial dysautonomia and Moebius syndrome.[47] Treatment involves techniques to manage stress and medications to control blood pressure. Preliminary data suggest that carbidopa, a DOPA decarboxylase inhibitor that does not cross the blood–brain barrier, may reduce norepinephrine surges and lessen blood pressure peaks.[48]

Catecholamine-Secreting Tumors s0195

p0365 Paragangliomas are rare neuroendocrine tumors derived from neural crest cells that arise in the peripheral ANS. Pheochromocytomas are paragangliomas that arise from chromaffin cells of the adrenal medulla. These are characterized by unpredictable paroxysmal episodes of excessive catecholamine secretion, resulting in hypertension, tachycardia, and headaches. Complications include arrhythmias, ventricular hypertrophy, and ischemia. Around 30% of pediatric patients have a genetic mutation (*SDHAF2*, *SDHB*, *SDHC*, and *SDHD* genes) or documented family history of pheochromocytoma/paraganglioma. Approximately 50% are malignant. Treatment is surgical.[49]

Autoimmune Autonomic Disorders s0200

p0370 The development of acute or subacute autonomic failure, frequently following a viral or bacterial infection, is believed to be the result of an autoimmune disorder. Autoimmune autonomic disorders can also be paraneoplastic (i.e., arising in patients with cancer). Immune cross-reactivity between tumor antigens and neurologic tissues may be the mechanism. These antibodies can target one or several sites of the nervous system, causing a wide variety of symptoms. Paraneoplastic syndromes are rare; they affect less than 1% of cancer patients, although the incidence in the pediatric population is unknown.[50] Paraneoplastic syndromes can appear before the clinical diagnosis of cancer is apparent, and therefore early diagnosis is vital.

Guillain-Barré Syndrome s0205

p0375 Guillain-Barré syndrome (GBS) is less common in children than in adults, with an incidence of 0.4 to 1.3 cases per 100,000 per year in children in the United States; it is rarely seen in children younger than 2 years old. GBS is responsible for most cases of acute and subacute flaccid paralysis in infants and children. Approximately two-thirds of patients diagnosed with GBS had a respiratory or gastrointestinal infection prior the start of the symptoms. Several viruses and bacteria have been linked to this syndrome. *Campylobacter jejuni* seems to be responsible for most of the GBS cases, although other microorganisms have been also reported. Autonomic instability with episodes of hypertension and hypotension and cardiac arrhythmia can occur. This can be life threatening, so close monitoring is required. Other autonomic symptoms such as gastrointestinal and bladder dysfunction can also be present.[51] Treatment includes intravenous immunoglobulin (IVIg) or plasma exchange.

Autoimmune Autonomic Ganglionopathy s0210

p0380 Autoimmune autonomic ganglionopathy is characterized by an acute-onset widespread sympathetic and parasympathetic

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

failure. Cholinergic deficits are pronounced and include severe impairment of gastrointestinal motility with gastroparesis and constipation, bladder retention, dry eyes, and dry mouth. Abnormal pupillary responses are common. Orthostatic hypotension can be severe.[52] There is no motor or sensory impairment. In 30% to 50% of patients, high titers of antibodies against the neuronal ganglionic nicotinic acetylcholine receptors (AChR) are identified. These antibodies block pre- to postganglionic neural traffic in sympathetic and parasympathetic ganglia. In the remaining cases, other autoantibodies not yet identified are the likely cause. Patients may respond to IVIg, plasma exchange, or rituximab, a monoclonal antibody that destroys B cells. This disorder has been largely described in patients with no identified cancer, although it has also been associated with malignancies. Some cases in children and adolescents have been reported, although its incidence in children is unknown.[53]

s0215 Acute Autonomic and Sensory Neuropathy

p0385 Acute autonomic ans sensory neuropathy is a rare disorder in which patients develop acute-onset fine-touch and proprioceptive sensory deficits leading to severe ataxia (sometimes referred to as pure sensory-type Guillain-Barre). Autonomic involvement includes neurogenic orthostatic hypotension and urinary and fecal incontinence. Plasma norepinephrine levels are low or undetectable. In most cases a gastrointestinal or respiratory infection precedes the neuropathy, suggesting an immune-mediated process,[54] in some cases resulting from antigalactocerebrosidase antibodies. IVIg and plasma exchange have been used, with varied success.

s0220 Anti-NMDA Receptor Encephalitis

p0390 Anti-NMDA receptor encephalitis results from antibodies against the NR1 and NR2 subunits of the NMDA receptor. Symptoms in children include behavioral and personality changes. As the diseases progresses, patients develop sleep disorders, seizures, movement disorders, and autonomic instability (tachycardia, hypertension, hypoventilation, urinary incontinence, and hypothermia or hyperthermia).[55] It has been linked to ovarian neoplasms, although it has been described in patients without cancer.

s0225 Lambert-Eaton Myasthenic Syndrome

p0395 In addition to weakness and reduced or absent deep tendon reflexes, autonomic dysfunction is a recognized feature of Lambert-Eaton myasthenic syndrome (LES). Dry mouth is the most frequent autonomic symptom, followed by sweating abnormalities and impaired cardiac parasympathetic reflexes.[56] The majority of patients have antibodies against PQ-type voltage-gated calcium channels (VGCC), and approximately 30% of patients have N-type VGCC autoantibodies. This syndrome is frequently found in association with small-cell carcinoma of the lung, but it has also been found in patients without neoplasms. Lambert-Eaton syndrome is very rare in children.[57]

s0230 Dipeptidyl-Peptidase-Like Protein-6 (DPPX) Potassium Channel Antibody Encephalitis

p0400 Dipeptidyl-peptidase-like protein-6 (DPPX) potassium channel antibody encephalitis, a recently described autoimmune encephalitis, affects adults and young teenagers and is characterized by the presence of antibodies against DPPX, a subunit of Kv4.2 potassium channels.[58] Main features are insidious and subacute cognitive impairment, abnormal eye movements, dysphagia, insomnia, and autonomic abnormalities, most prominently gastrointestinal symptoms (diarrhea, gastroparesis, constipation), followed by urinary symptoms, fluctuating hyperthermia/hypothermia, and asymptomatic ventricular tachycardia. In fact, antibodies from patients' serum bind avidly to ganglionic neurons in the myenteric plexus of the gut.[58] Some of the patients with DPPX antibodies also had B-cell neoplasms, gastrointestinal lymphoma, and chronic lymphocytic leukemia.

Genetic Autonomic Disorders s0235

There are a number of rare, early-onset genetic disorders that affect the ANS. Although the extent of autonomic involvement varies, certain genetic conditions are associated with widespread autonomic dysfunction. p0405

Hereditary Sensory and Autonomic Neuropathies s0240

Hereditary sensory and autonomic neuropathies (HSANs) are a group of rare disorders caused by different mutations that affect different aspects of the development, function, or survival of sensory and autonomic neurons. Initially classified according to age of onset, mode of inheritance, and predominant clinical features, diagnosis is now based on identifying pathogenic mutations. Classification is evolving as a result of the discovery of increasing numbers of mutations and the availability of whole-exome sequencing (Table 154-2). For each HSAN type, penetrance is complete, but phenotypic expression varies markedly. Impaired pain and temperature perception are common traits. p0410

HSAN Type 1. HSAN type 1 is the most common HSAN, but it is an adult-onset disorder. Patients have varying degrees of sensorineural hearing loss, distal anhidrosis, and episodes of lancinating pain in the limbs. HSAN type 1 is further classified into subtypes A through F based on the locus of the gene mutation and clinical phenotype[59–61] (Table 154-2). s0245 p0415

HSAN Type 2. HSAN type 2 is an autosomal-recessive disorder characterized by impaired temperature, pain, and fine-touch sensation. Onset varies from birth up until the beginning of the teens. There are at least four causative gene mutations resulting in subsequent subtype designations (A through D); some of them are particularly common in the French Canadian population. Autonomic involvement is not well defined and varies markedly. Autonomic dysfunction is also variable[62–64] (Table 154-2). s0250 p0420

HSAN Type 3 (Familial Dysautonomia). HSAN type 3 (familial dysautonomia, OMIM# 223900) is an autosomal-recessive disease almost exclusively affecting children with Eastern European Jewish ancestry.[65] Over 99% of affected patients are homozygous for the founder point mutation (6T>C change) in the gene encoding for the elongator-1 protein (ELP-1), known also as I-κ B kinase-associated protein (IKAP).[66] IKAP (ELP-1) is expressed in most cells throughout the body.[67] The deficiency of IKAP (ELP-1) during embryogenesis affects the development of primary sensory (i.e., afferent) neurons that carry information to the CNS with cell bodies in the dorsal root and cranial nerve ganglia. Efferent (motor) neurons are mostly spared. s0255 p0425

In contrast to other HSANs, in HSAN type 3, autonomic dysfunction dominates the clinical picture. The main autonomic defect in patients with HSAN type 3 is in the afferent (sensory) neurons that convey incoming information from the arterial baroreceptors, resulting in the unusual combination of orthostatic hypotension and paroxysmal hypertension.[47] Although reduced in number, the efferent sympathetic nerves are functionally active, and their effects are magnified because of denervation supersensitivity. Supine plasma p0430

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

t0015 **TABLE 154-2** Hereditary Sensory and Autonomic Neuropathies

Type	Gene	Inheritance	Onset	Autonomic Features	Sensory Features	Other Features
HSAN 1A	SPTLC1	AD	Adult	Varying degrees of distal anhidrosis	Progressive loss of pain, temperature, and fine-touch sensation Varying degrees of sensorineural hearing loss Episodes of lancinating limb pain	One case with congenital presentation reported with severe growth and mental retardation, microcephaly, hypotonia, and respiratory insufficiency
HSAN 1B	3p24-p22 locus					Cough and gastroesophageal reflux
HSAN 1C	SPTLC2					Varying degrees of distal muscle weakness
HSAN 1D	ALT1			None		—
HSAN 1E	DMNT1			None		Early-onset dementia
HSAN 1F	ATL3			None		—
HSAN 2A	WNK1	AR	Childhood or adolescence	None	Varying degrees of progressive loss of pain, temperature, and fine-touch sensation	—
HSAN 2B	FAM134B			Varying degrees of hyperhidrosis, urinary incontinence, and pupillary abnormalities		
HSAN 2C	KIF1A			None		—
HSAN 2D	SCN9A			Urinary and fecal incontinence, reduced sweating		Lack of fungiform lingual papillae, hyposmia, hearing loss, hypogeusia, and bone dysplasia
HSAN 3	IKAP (ELP-1)	AR	Newborn	Impaired lacrimation Orthostatic hypotension Paroxysmal hypertension and vomiting episodes with skin blotching Normal or increased sweating	Impaired pain and temperature sensation with preserved fine-touch sensation	Described in Ashkenazi Jewish ancestry Neonatal hypotonia Respiratory and feeding difficulties Neuropathic joints Optic neuropathy Chronic lung disease Scoliosis Rhabdomyolysis Renal failure Varying degrees of cognitive and behavioral problems
HSAN 4	NTRK (TRKA)	AR	Newborn	Anhidrosis Episodic hyperthermia Undetectable plasma norepinephrine	Loss of pain and temperature sensation Preserved fine touch and vibration sensation	Frequent fractures Neuropathic joints Slow-healing wounds Varying degrees of cognitive and behavioral problems
HSAN 5	NGFβ	AR	Newborn	Variable degree of anhidrosis	Loss of pain and temperature sensation Preserved fine-touch and vibration sensation	Frequent fractures Neuropathic joints Tooth loss from gingival disease
HSAN 6	DST	AR	Newborn	Impaired lacrimation Labile blood pressure and heart rate Hyperthermia and skin-blotching episodes	Loss of pain and temperature sensation	Described in Ashkenazi Jewish ancestry Neonatal hypotonia Respiratory and feeding difficulties, delayed psychomotor development, neuropathic joints All described patients died before age 3
HSAN 7	SCN11A	AD (only a heterozygous de novo mutation described)	Newborn	Hyperhidrosis and gastrointestinal dysfunction	Loss of pain and temperature sensation	Frequent fractures Neuropathic joints Slow-healing wounds

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

norepinephrine levels are normal. Stimuli that activate efferent sympathetic neurons, independently of baroreceptor afferent pathways, such as cognitive tasks and emotional arousal, dramatically increase blood pressure, heart rate, and circulating norepinephrine levels.[47]

p0435 Episodic retching and vomiting attacks accompanied by skin blotching, diaphoresis, hypertension, and tachycardia ("dysautonomic crises") are common. These are the result of sudden increases in circulating catecholamines that are unrestrained by baroreceptor feedback.[47] End-organ target damage (e.g., chronic kidney disease) occurs as a long-term consequence of hypertension and excessive blood pressure variability.

p0440 Superficial pain perception is severely decreased, but patients complain of abdominal discomfort and or bone pain following fractures or surgical procedures, suggesting that some visceral pain perception is preserved. Corneal analgesia often results in abrasions and ulcerations complicated by alacrima. Patients with HSAN type 3 have been shown to have a specific type of optic neuropathy that resembles mitochondrial neuropathies.[68]

p0445 Gait ataxia and incoordination, resulting from a lack of muscle spindle afferents, affect patients from birth and progressively worsen over time.[69] Other features include feeding problems resulting from neurogenic dysphagia, failure to thrive, and increased frequency of rhabdomyolysis.[70] Cognitive and behavioral issues, such as anxiety, reduced IQ, emotional overreaction, and emotional rigidity, prevent many patients from living independently.[71] Abnormal spinal curvature, corrective spinal surgery, depressed ventilatory drive, sleep-disordered breathing, and frequent aspirations compromise respiratory function. The incidence of sudden death, particularly during sleep, is increased.

p0450 Therapeutic focus in HSAN type 3 is on reducing the catecholamine surges caused by blunted baroreceptor feedback (i.e., afferent baroreflex failure). Carbidopa is frequently used to block dopamine production outside the CNS and prevent dopamine-induced vomiting.[5]

p0455 Additional therapeutic measures include management of neurogenic dysphagia, early treatment of aspiration pneumonias, and noninvasive ventilatory support during sleep. Clinical trials of compounds that increase levels of IKAP (ELP-1) are under way.[72]

s0260 p0460 **HSAN Type 4 (Congenital Insensitivity to Pain with Anhidrosis).** HSAN type 4 (OMIM #256800) is an autosomal-recessive disorder first described in children with mental retardation, insensitivity to pain, self-mutilating behavior, and unexplained fevers. A cardinal feature of the disease is complete anhidrosis in response to thermal, emotional, or direct stimulation of the skin.[73] Self-mutilation is extremely common. Pinprick sensation is also diminished. Skin wounds and bone injuries heal poorly. Joints are susceptible to repeated trauma, resulting in neuropathic joints and osteomyelitis. Avoidance of harmful stimuli is crucial to prevent recurrent injuries but is frequently difficult to accomplish because patients usually have intellectual disability with impulsivity and reckless behaviors.

p0465 HSAN type 4 is associated with missense, nonsense, and frame-shift mutations in the gene that encodes for the neurotrophic tyrosine kinase-1 receptor (NTRK, previously known as TRK or TRKA).[74] NTRK is normally expressed on specific neurons in the peripheral and central nervous systems and forms part of the high-affinity receptor of nerve growth factor (NGF). Failure to express the tyrosine kinase receptor affects the normal development of sympathetic nerves, nociceptive neurons of the dorsal root ganglia, and the ascending cholinergic neurons of the basal forebrain, which are all dependent on NGF signaling. Skin biopsies of patients with HSAN type 4 reveal that sweat glands are preserved, but they lack sympathetic cholinergic innervation, thus the anhidrosis, which can lead to hyperthermia and death.[75]

p0470 Patients with HSAN type 4 have very low or undetectable levels of circulating norepinephrine but normal epinephrine levels, suggesting that lack of NTRK-NGF signaling affects the development of sympathetic adrenergic neurons but spares chromaffin cells in the adrenal medulla.[76] Interestingly, despite the very low norepinephrine levels indicating impaired or absent sympathetic activity, patients with HSAN type 4 have normal cardiovascular responses to orthostatic stress.[76] Prognosis is largely unknown.

s0265 p0475 **HSAN Type 5.** Patients with HSAN type 5 (OMIM # 608654) respond normally to touch, pressure, and vibration, but have a selective loss of temperature and pain sensation, leading to painless fractures, bone necrosis, and neuropathic joints. The have variable degrees of sweating impairment (ranging from normal sweating to anhidrosis).[77] The disorder is caused by homozygous mutations in the nerve growth factor β (NGFB) gene. Heterozygous carriers can present in adulthood with a mild phenotype.[78]

s0270 p0480 **HSAN Type 6.** Reported in a large consanguineous Ashkenazi Jewish family,[79] HSAN type 6 is a severe autosomal recessive disorder resulting from homozygous truncating mutations in the dystonin gene (OMIM #614653). The disorder is characterized by neonatal hypotonia, areflexia, respiratory and feeding difficulties, delayed psychomotor development, neuropathic joints, labile blood pressure and heart rate, and lack of corneal reflexes. All patients have died before age 3.

s0275 p0485 **HSAN Type 7.** Reported in two unrelated patients (OMIM # 615548), HSAN type 7 includes the clinical features of congenital insensitivity to pain resulting in self-mutilations, slow-healing wounds, painless fractures, hyperhidrosis and gastrointestinal dysfunction requiring parenteral nutrition. The disorder results from de novo heterozygous missense mutations in the *SCN11A* gene.[80]

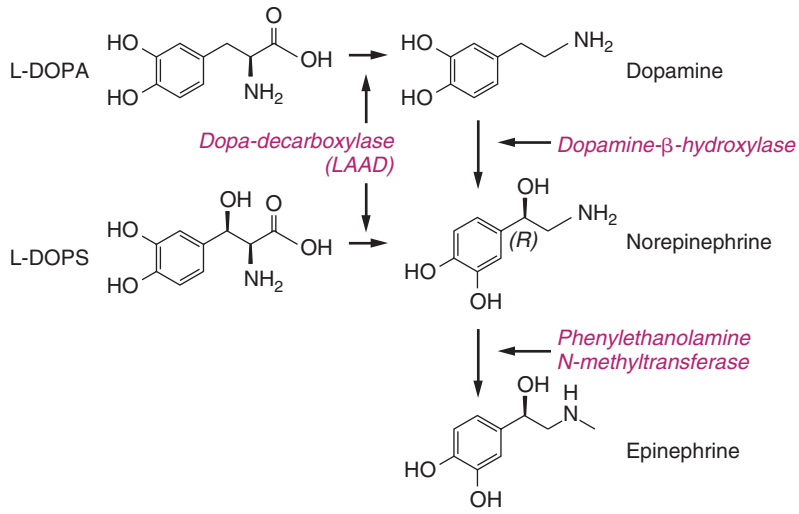
s0280 p0490 **Other Syndromes with Sensory and Autonomic Involvement.** *Navajo familial neurogenic arthropathy* was initially described in Native American (Navajo) children. It is characterized by diminished or absent sweating with variable sensory deficits, ranging from insensitivity to pain (leading to fractures, corneal injuries, and neuropathic joints) to normal sensation.[81] Self-mutilating behaviors are typically absent.

p0495 *Stuve-Wiedemann syndrome* (OMIM #601559), also known as neonatal Schwartz-Jampel syndrome type 2 (SJS2), is an autosomal-recessive disorder caused by mutations in the LIFR gene.[82] It is characterized by bowing of the lower limbs, wide metaphyses with abnormal trabecular pattern, and camptodactyly (one or more fingers permanently bent as a result of fixed-flexion deformity of the proximal interphalangeal joints). Additional features include feeding and swallowing difficulties, respiratory distress, and episodes of hyperthermia, which can be fatal in the first months of life. Survivors develop progressive scoliosis and spontaneous fractures. Sensory abnormalities, including decreased sensitivity to pain and temperature, lead to corneal injury and absent deep tendon reflexes. Cognition and behavior appear to be normal. Hypertrichosis is common.

Inborn Errors of Metabolism s0285

s0290 p0500 **Dopamine Beta-Hydroxylase Deficiency.** Dopamine beta-hydroxylase deficiency, a rare disorder, is caused by mutations in the gene encoding the enzyme dopamine beta-hydroxylase (DBH), which converts dopamine to norepinephrine (NE)

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324



f0040

Figure 154-7. Catecholamine pathways. Droxidopa (L-DOPS) converts to norepinephrine as a result of the action of the enzyme dopa-decarboxylase (L-amino acid aromatic decarboxylase). This is the same enzyme that converts L-DOPA to dopamine.

(OMIM # 223360). Affected patients have undetectable levels of plasma NE and epinephrine, with increased dopamine levels (indicative of a "bottleneck" in the catecholamine pathways; Figure 154-7). Newborns can show a delay in eye opening and palpebral ptosis. Hypotension, hypoglycemia, and hypothermia may occur early in life. The absence of norepinephrine leads to deficient vasoconstriction, resulting in hypotension, syncope, and reduced exercise capacity. Symptoms generally worsen in late adolescence and early adulthood.[83] Additional features include nasal stuffiness and prolonged or retrograde ejaculation. Treatment with droxidopa (Northera®), a synthetic norepinephrine precursor, replenishes norepinephrine, increases blood pressure, and improves symptoms of hypotension.[84]

s0295 p0505 **Aromatic L-Amino Acid Decarboxylase Deficiency.** Aromatic L-amino acid decarboxylase deficiency, an extremely rare autosomal recessive disorder, is caused by mutations in the *DDC* gene. The enzyme aromatic L-amino acid decarboxylase (AADC) converts L-dopa and 5-hydroxytryptophan to dopamine and serotonin, respectively (OMIM #608643). Neonatal symptoms include poor feeding, lethargy, ptosis, hypothermia, hypotension, intermittent eye movement abnormalities (oculogyric crises), hypotonia, and motor symptoms such as rigidity and difficulty with movements. Behavioral problems include emotional lability and irritability. Diagnosis is based on measurement of AADC activity in plasma and *DDC* gene sequencing. Increased levels of urinary vanillactic acid (VLA) are diagnostic. Treatment is aimed at correcting the neurotransmitter abnormalities with different medications (dopamine agonists, monoaminoxidase inhibitors, selective serotonin reuptake inhibitors, pyridoxine, droxidopa, 5-hydroxytriptophan, etc.).[85]

s0300 p0510 **Menkes Disease.** Menkes disease, also known as kinky hair disease, is an X-linked neurodegenerative disease of impaired copper transport. It is caused by mutations in the *ATP7A* gene (OMIM #309400). Children usually present at 2 to 3 months of age with loss of developmental milestones, failure to thrive, truncal hypotonia, and epileptic and myoclonic seizures. Milder variants with minimal neurologic features with normal or almost normal intelligence have been described. Autonomic abnormalities are not well characterized, although orthostatic hypotension and chronic diarrhea have been reported.[86] Decreased serum copper and serum ceruloplasmin levels can be useful in the differential diagnosis. Decreased NE levels have been found. An elevated hydroxyphenylalanine (DOPA) and dihydroxyphenylglycol (DHPG) ratio resulting from decreased activity of DBH may be observed, with higher values reflecting more severe disease. Treatment with droxidopa can be useful.[87]

s0305 p0515 **Fabry Disease.** Fabry disease, an X-linked inborn error of glycosphingolipid catabolism, is caused by mutations in the *GLA* gene, resulting in deficient or absent activity of the lysosomal enzyme alpha-galactosidase A (OMIM # 301500). This leads to systemic accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in plasma and organ cells throughout the body, including autonomic and dorsal root ganglia. Clinical manifestations begin in childhood or adolescence and include severe neuropathic or limb pain, telangiectasias and angiokeratomas, and renal manifestations. Symptoms of autonomic dysfunction include sweating abnormalities (hypohidrosis or hyperhidrosis), decreased lacrimation, decreased salivation, and gastrointestinal dysmotility.[88] The degree of cardiovascular autonomic involvement is unclear.

s0310 p0520 **Porphyrias.** Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria (OMIM #176000) is the most common form of porphyria and is inherited in an autosomal-dominant manner. It is caused by mutations affecting the gene encoding hydroxymethylbilane synthase (HMBS). It is characterized by acute, recurrent episodes of abdominal pain, gastrointestinal dysfunction, and neurologic impairment. Patients are asymptomatic in between episodes. Autonomic abnormalities include tachycardia, hypotension, urinary retention, and gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation).[89] Other clinical features include facial weakness, dysphagia, psychosis, depression, dementia, and seizures. Acute attacks rarely occur before puberty, are more common in women, and can be precipitated by barbiturates, sulfonamides, alcohol, infection, starvation, and hormonal changes. Increased urinary excretion of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) during the attacks supports the diagnosis.

p0525 Porphyria variegata (OMIM #176200) is also an autosomal-dominant disorder and is caused by heterozygous mutations in the gene encoding for protoporphyrinogen oxidase (PPOX). The clinical features are similar to those of acute intermittent

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

porphyria, but with an increased frequency of skin photosensitivity and hypertrichosis.

s0315 Hirschsprung Disease

p0530 Also known as aganglionic megacolon, Hirschsprung disease is characterized by congenital absence of ganglionic cells in the myenteric (Auerbach) and submucosal (Meissner) plexuses of the gastrointestinal tract. Affected patients have severe gastroparesis, leading to partial or complete bowel obstruction and dilation of the colon. Cardiovascular autonomic dysfunction has been described. Mutations in the *RET* gene and several other identified loci increase susceptibility to the disorder.[90] Hirschsprung disease also occurs as a feature of several syndromes, including Waardenburg-Shah syndrome, Mowat-Wilson syndrome, Goldberg-Shprintzen syndrome, and congenital central hypoventilation syndrome. Heterozygous mutations in the *ECE1* gene (OMIM #613870) cause Hirschsprung disease with cardiac defects and autonomic dysfunction (episodes of severe agitation in association with tachycardia, hypertension, and hyperthermia).[91]

s0320 Congenital Central Hypoventilation Syndrome and Related Ventilatory Disorders

p0535 Congenital central hypoventilation syndrome (CCHS; OMIM #209880) is an autosomal-dominant disorder most commonly caused by mutations in the *PHOX2B*, *RET*, *GDNF*, *EDN3*, *ASCL1*, and *BDNF* genes.[92] Also known as "Ondine's curse," CCHS is a rare disorder characterized by abnormal control of respiration in the absence of neuromuscular, lung, or cardiac disease, or identifiable brainstem lesions. Hypoventilation is usually more prominent at night but can occur during the day in severe cases. These patients typically present in the first hours of life with cyanosis and increased hypercapnia during sleep. They have an impairment of ventilatory and arousal responses to both hypercapnia and hypoxemia. Children with CCHS often have additional autonomic symptoms, including severe constipation, dysphagia, pupillary abnormalities, and decreased body temperature. Sympathetic activity may be exaggerated.[93]

p0540 Pitt-Hopkins syndrome (OMIM # 610954), caused by heterozygous (sometimes de novo) mutations of the *TCF4* gene, is characterized by abnormal psychomotor development, distinctive facial features, microcephalia, clubbing, and intermittent hyperventilation followed by apnea during both wakefulness and sleep.

s0325 Allgrove Syndrome and Related Disorders

p0545 Also known as achalasia-addisonianism-alacrima syndrome, and triple-A syndrome, Allgrove syndrome is caused by mutations in the gene encoding the protein aladin (*AAAS*; OMIM #231550). It is inherited in a recessive fashion. Children present with classic symptoms of primary adrenal insufficiency, including hypoglycemic seizures and shock. Less frequently, they present with recurrent vomiting, dysphagia, and failure to thrive or ocular symptoms associated with alacrima. At presentation, review of systems may also be positive for crying without tears, hyperpigmentation, developmental delay, seizures, hypernasal speech, and symptoms related to orthostatic hypotension.[94]

p0550 Alacrima, achalasia, and mental retardation (AAMR) syndrome is an autosomal-recessive disorder caused by homozygous mutations in the *GMPPA* gene and characterized by onset of features at birth or in early infancy. More variable features include hypotonia, gait abnormalities, anisocoria, and visual or hearing deficits. Patients with AAMR do not have adrenal insufficiency.[95]

Other Genetic Disorders with Autonomic Dysfunction s0330

T54

Rett Syndrome. Rett syndrome is a neurodevelopmental disorder that occurs almost exclusively in females. It is characterized by arrested development between 6 and 18 months of age, regression of acquired skills, loss of speech, stereotypic movements (classically of the hands), microcephaly, seizures, and cognitive impairment. Autonomic dysfunction results in abnormal, irregular breathing during wakefulness and sleep, including hyperventilation, hypoventilation, and apnea; abnormal heart-rate variability; and labile blood pressure with episodic hypertension and tachycardia. Almost a third of all deaths from Rett syndrome are sudden and unexpected, which has been linked to autonomic dysregulation. s0335 p0555 3

Alexander Disease. Alexander disease, an autosomal-dominant disease, is caused by mutations (usually de novo) in the gene encoding glial fibrillary acidic protein (*GFAP*; OMIM # 203450). The disorder is subclassified as infantile, juvenile, or adult onset. Patients present with seizures, megalencephaly, developmental delay, and spasticity. They can go on to develop early-onset dementia and ataxia. They have early signs of autonomic dysfunction, including constipation, episodic hypothermia, and sleep-disordered breathing. Adult patients can develop orthostatic hypotension and erectile dysfunction.[96] Brain MRI typically shows cerebral white-matter abnormalities affecting the frontal region; brainstem and cerebellar atrophy also can be present. s0340 p0560

Hyperbradykininism. Hyperbradykininism is an autosomal-dominant disorder characterized by orthostatic hypotension (leading to lightheadedness upon standing and syncope), facial erythema, and purple discoloration of the legs after standing. Plasma bradykinin is elevated.[97] s0345 p0565

Panayiotopoulos Syndrome. Panayiotopoulos syndrome is a form of idiopathic benign childhood focal epilepsy in which the seizures are associated with signs of increased autonomic activity. It affects 13% of children aged 3 to 6 years who have had at least one afebrile seizure. Seizures are accompanied by vomiting, diaphoresis, skin vasomotor changes, hypersalivation, lacrimation, and gastrointestinal discomfort. Recent reports document hypertension, tachycardia, and release of vasopressin during the seizures, suggestive of activation of the central autonomic network.[98] In rare cases, respiratory and cardiac arrest have been reported. Mutations in the *SCN1A* gene increase susceptibility for this disorder.[99] s0350 p0570

Congenital Alacrima. Children with congenital alacrima have markedly deficient lacrimation from infancy, leading to corneal epithelial lesions, presumably as a result of hypoplasia of the lacrimal glands. Genetic mutations have not yet been identified. s0355 p0575

Cold-Induced Sweating Syndrome. Cold-induced sweating syndrome, an autosomal-recessive disorder, presents in the neonatal period with orofacial weakness and feeding difficulties related to impaired sucking and swallowing. Affected infants show a tendency to startle, trismus, sialorrhea, and opisthotonus. During the first year, most infants have episodes of unexplained fever. After the first 2 years, abnormal muscle contractions and fevers improve, and most patients show normal psychomotor development. From childhood onward, the most disabling symptoms stem from impaired thermoregulation. Patients have hyperhidrosis, mainly of the upper body, in response to cold temperatures, and sweat very little with heat. The disorder is caused by homozygous or compound heterozygous mutations in the *CRLF1* gene or in the *CLCF1* gene (OMIM #272430 and # 610313).[100] s0360 p0580

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

REFERENCES

1. Kreibig SD. Autonomic nervous system activity in emotion: a review. Biol Psychol 2010;84(3):394–421. PubMed PMID: 20371374.
2. Langley JN. On the Union of Cranial Autonomic (Visceral) Fibres with the Nerve Cells of the Superior Cervical Ganglion. J Physiol 1898;23(3):240–70. PubMed PMID: 16992456. Pubmed Central PMCID: 1516595.
3. Wieling W, Thijs RD, van Dijk N, et al. Symptoms and signs of syncope: a review of the link between physiology and clinical clues. Brain 2009;132(Pt 10):2630–42. PubMed PMID: 19587129.
4. Norcliffe-Kaufmann LJ, Kaufmann H, Hainsworth R. Enhanced vascular responses to hypocapnia in neurally mediated syncope. Ann Neurol 2008;63(3):288–94. PubMed PMID: 17823939.
5. Norcliffe-Kaufmann L, Martinez J, Axelrod F, et al. Hyperdopaminergic crises in familial dysautonomia: a randomized trial of carbidopa. Neurology 2013;80(17):1611–17. PubMed PMID: 23553478. Pubmed Central PMCID: 3662326.
6. Franco I. Pediatric overactive bladder syndrome: pathophysiology and management. Paediatr Drugs 2007;9(6):379–90. PubMed PMID: 18052408.
7. Neveus T, Sillen U. Lower urinary tract function in childhood; normal development and common functional disturbances. Acta Physiol (Oxf) 2013;207(1):85–92. PubMed PMID: 23088436.
8. So HK, Li AM, Au CT, et al. Night sweats in children: prevalence and associated factors. Arch Dis Child 2012;97(5):470–3. PubMed PMID: 21427123.
9. Gridina I, Bidat E, Chevallier B, et al. [Prevalence of chronic hyperventilation syndrome in children and teenagers]. Arch Pediatr 2013;20(3):265–8. PubMed PMID: 23375424. Prevalence du syndrome d'hyperventilation chronique chez les enfants et les adolescents.
10. Freeman R, Chapleau MW. Testing the autonomic nervous system. Handb Clin Neurol 2013;115:115–36. PubMed PMID: 23931777.
11. el Bedawi KM, Hainsworth R. Combined head-up tilt and lower body suction: a test of orthostatic tolerance. Clin Auton Res 1994;4(1–2):41–7. PubMed PMID: 8054836.
12. Tellez MJ, Norcliffe-Kaufmann LJ, Lenina S, et al. Usefulness of tilt-induced heart rate changes in the differential diagnosis of vasovagal syncope and chronic autonomic failure. Clin Auton Res 2009;19(6):375–80. PubMed PMID: 19834645.
13. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21(2):69–72. PubMed PMID: 21431947. Epub 2011/03/25. eng.
14. Ganzeboom KS, Colman N, Reitsma JB, et al. Prevalence and triggers of syncope in medical students. Am J Cardiol 2003;91(8):1006–8, A8. PubMed PMID: 12686351.
15. Colman N, Nahm K, Ganzeboom KS, et al. Epidemiology of reflex syncope. Clin Auton Res 2004;14(Suppl. 1):9–17. PubMed PMID: 15480937.
16. Kaufmann H, Hainsworth R. Why do we faint? Muscle Nerve 2001;24(8):981–3.
17. Kaufmann H, Saadia D, Voustianiouk A. Midodrine in neurally mediated syncope: a double-blind, randomized, crossover study. Ann Neurol 2002;52(3):342–5. PubMed PMID: 12205647.
18. el-Bedawi KM, Wahbha MA, Hainsworth R. Cardiac pacing does not improve orthostatic tolerance in patients with vasovagal syncope. Clin Auton Res 1994;4(5):233–7. PubMed PMID: 7888741.
19. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc 2012;87(12):1214–25. PubMed PMID: 23122672. Pubmed Central PMCID: 3547546.
20. Gibbons CH, Bonyhay I, Benson A, et al. Structural and functional small fiber abnormalities in the neuropathic postural tachycardia syndrome. PLoS ONE 2013;8(12):e84716. PubMed PMID: 24386408. Pubmed Central PMCID: 3874039.
21. Corkal JC, Kimpinski K. A prospective study of excessive postural heart rate change on head-up tilt. Clin Auton Res 2014;24(6):253–8. PubMed PMID: 25270997.
22. Raj SR. Postural tachycardia syndrome (POTS). Circulation 2013;127(23):2336–42. PubMed PMID: 23753844. Pubmed Central PMCID: 3756553.
23. Parsaik AK, Singer W, Allison TG, et al. Orthostatic intolerance without postural tachycardia: how much dysautonomia? Clin Auton Res 2013;23(4):181–8. PubMed PMID: 23729158. Pubmed Central PMCID: 3902804.
24. Benrud-Larson LM, Sandroni P, Haythornthwaite JA, et al. Correlates of functional disability in patients with postural tachycardia syndrome: preliminary cross-sectional findings. Health Psychol 2003;22(6):643–8. PubMed PMID: 14640863.
25. Crocker MK, Yanovski JA. Pediatric obesity: etiology and treatment. Pediatr Clin North Am 2011;58(5):1217–40, xi. PubMed PMID: 21981957. Pubmed Central PMCID: 3260452.
26. Liao D, Rodriguez-Colon SM, He F, et al. Childhood obesity and autonomic dysfunction: risk for cardiac morbidity and mortality. Curr Treat Options Cardiovasc Med 2014;16(10):342. PubMed PMID: 25143120. Pubmed Central PMCID: 4159679.
27. Rodriguez-Colon S, He F, Bixler EO, et al. The circadian pattern of cardiac autonomic modulation and obesity in adolescents. Clin Auton Res 2014;24(6):265–73. PubMed PMID: 25358502. Pubmed Central PMCID: 4267540.
28. Jarrin DC, McGrath JJ, Poirier P, et al. Autonomic dysfunction: a possible pathophysiological pathway underlying the association between sleep and obesity in children at-risk for obesity. J Youth Adolesc 2015;44(2):285–97. PubMed PMID: 25480401.
29. Rodriguez-Colon SM, He F, Bixler EO, et al. Metabolic syndrome burden in apparently healthy adolescents is adversely associated with cardiac autonomic modulation-Penn State Children Cohort. Metabolism 2015 Feb 3. PubMed PMID: 25684658.
30. Feber J, Ruzicka M, Geier P, et al. Autonomic nervous system dysregulation in pediatric hypertension. Curr Hypertens Rep 2014;16(5):426. PubMed PMID: 24633841.
31. DiMario FJ Jr, Dunham B, Burleson JA, et al. An evaluation of autonomic nervous system function in patients with Prader-Willi syndrome. Pediatrics 1994;93(1):76–81. PubMed PMID: 8265328.
32. Ize-Ludlow D, Gray JA, Sperling MA, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics 2007;120(1):e179–88. PubMed PMID: 17606542.
33. Rosen DS, American Academy of Pediatrics Committee on A. Identification and management of eating disorders in children and adolescents. Pediatrics 2010;126(6):1240–53. PubMed PMID: 21115584.
34. Dippacher S, Willaschek C, Buchhorn R. Different nutritional states and autonomic imbalance in childhood. Eur J Clin Nutr 2014;68(11):1271–3. PubMed PMID: 25248356.
35. Takimoto Y, Yoshiuchi K, Ishizawa T, et al. Autonomic dysfunction responses to head-up tilt in anorexia nervosa. Clin Auton Res 2014;24(4):175–81. PubMed PMID: 24969228.
36. Mont L, Castro J, Herreros B, et al. Reversibility of cardiac abnormalities in adolescents with anorexia nervosa after weight recovery. J Am Acad Child Adolesc Psychiatry 2003;42(7):808–13. PubMed PMID: 12819440.
37. Murialdo G, Casu M, Falchero M, et al. Alterations in the autonomic control of heart rate variability in patients with anorexia or bulimia nervosa: correlations between sympathovagal activity, clinical features, and leptin levels. J Endocrinol Invest 2007;30(5):356–62. PubMed PMID: 17598965.
38. Verrotti A, Loiacono G, Mohn A, et al. New insights in diabetic autonomic neuropathy in children and adolescents. Eur J Endocrinol 2009;161(6):811–18. PubMed PMID: 19734243.
39. Trotta D, Verrotti A, Salladini C, et al. Diabetic neuropathy in children and adolescents. Pediatr Diabetes 2004;5(1):44–57.
40. Verrotti A, Chiarelli F, Blasetti A, et al. Autonomic neuropathy in diabetic children. J Paediatr Child Health 1995;31(6):545–8.
41. Uysal F, Ozboyaci E, Bostan O, et al. Evaluation of electrocardiographic parameters for early diagnosis of autonomic dysfunction in children and adolescents with type-1 diabetes mellitus. Pediatr Int 2014;56(5):675–80. PubMed PMID: 24617770.
42. Palma JA, Benarroch EE. Neural control of the heart: Recent concepts and clinical correlations. Neurology 2014 Jun 13. PubMed PMID: 24928126.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

43. Kirk KA, Shoykhet M, Jeong JH, et al. Dysautonomia after pediatric brain injury. Dev Med Child Neurol 2012;54(8):759–64. PubMed PMID: 22712762. Pubmed Central PMCID: 3393822.
44. Parent S, Mac-Thiong JM, Roy-Beaudry M, et al. Spinal cord injury in the pediatric population: a systematic review of the literature. J Neurotrauma 2011;28(8):1515–24. PubMed PMID: 21501096. Pubmed Central PMCID: 3143390.
45. Krassioukov A, Warburton DE, Teasell R, et al. A systematic review of the management of autonomic dysreflexia after spinal cord injury. Arch Phys Med Rehabil 2009;90(4):682–95. PubMed PMID: 19345787. Pubmed Central PMCID: 3108991.
46. Robertson D, Hollister AS, Biaggioni I, et al. The diagnosis and treatment of baroreflex failure. N Engl J Med 1993;329(20):1449–55. PubMed PMID: 8413455.
47. Norcliffe-Kaufmann L, Axelrod F, Kaufmann H. Afferent baroreflex failure in familial dysautonomia. Neurology 2010;75(21):1904–11. PubMed PMID: 21098405. Epub 2010/11/26. eng.
48. Norcliffe-Kaufmann L, Palma JA, Martinez J, et al. Carbidopa: A Novel Approach to Treating Paroxysmal Hypertension in Afferent Baroreflex Failure. Neurology 2014;82(10):P1.089.
49. Pham TH, Moir C, Thompson GB, et al. Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. Pediatrics 2006;118(3):1109–17. PubMed PMID: 16951005.
50. Wells EM, Dalmau J. Paraneoplastic neurologic disorders in children. Curr Neurol Neurosci Rep 2011;11(2):187–94. PubMed PMID: 21161703. English.
51. Rosen BA. Guillain-Barré Syndrome. Pediatr Rev 2012;33(4):164–71.
52. Vernino S, Hopkins S, Wang Z. Autonomic ganglia, acetylcholine receptor antibodies, and autoimmune ganglionopathy. Auton Neurosci 2009;146(1–2):3–7. PubMed PMID: 18951069. Pubmed Central PMCID: 2677210.
53. Fischer PR, Sandroni P, Pittock SJ, et al. Isolated sympathetic failure with autoimmune autonomic ganglionopathy. Pediatr Neurol 2010;43(4):287–90. PubMed PMID: 20837310.
54. Koike H, Atsuta N, Adachi H, et al. Clinicopathological features of acute autonomic and sensory neuropathy. Brain 2010;133(10):2881–96. PubMed PMID: 20736188.
55. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66(1):11–18. PubMed PMID: 19670433. Pubmed Central PMCID: 2826225.
56. O'Suilleabhain P, Low PA, Lennon VA. Autonomic dysfunction in the Lambert-Eaton myasthenic syndrome: serologic and clinical correlates. Neurology 1998;50(1):88–93. PubMed PMID: 9443463.
57. Morgan-Followell B, de Los Reyes E. Child neurology: diagnosis of Lambert-Eaton myasthenic syndrome in children. Neurology 2013;80(21):e220–2. PubMed PMID: 23690300.
58. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology 2014;83(20):1797–803. PubMed PMID: 25320100. Pubmed Central PMCID: 4240433.
59. Auer-Grumbach M. Hereditary sensory neuropathy type I. Orphanet J Rare Dis 2008;3:7. PubMed PMID: 18348718. Pubmed Central PMCID: 2311280. Epub 2008/03/20. eng.
60. Rotthier A, Auer-Grumbach M, Janssens K, et al. Mutations in the SPTLC2 subunit of serine palmitoyltransferase cause hereditary sensory and autonomic neuropathy type I. Am J Hum Genet 2010;87(4):513–22. PubMed PMID: 20920666. Pubmed Central PMCID: 2948807.
61. Klein CJ, Bird T, Ertekin-Taner N, et al. DNMT1 mutation hot spot causes varied phenotypes of HSAN1 with dementia and hearing loss. Neurology 2013;80(9):824–8. PubMed PMID: 23365052. Pubmed Central PMCID: 3598458.
62. Roddier K, Thomas T, Marleau G, et al. Two mutations in the HSN2 gene explain the high prevalence of HSAN2 in French Canadians. Neurology 2005;64(10):1762–7. PubMed PMID: 15911806. Epub 2005/05/25. eng.
63. Riviere JB, Ramalingam S, Lavastre V, et al. KIF1A, an axonal transporter of synaptic vesicles, is mutated in hereditary sensory and autonomic neuropathy type 2. Am J Hum Genet 2011;89(2):219–30. PubMed PMID: 21820098. Pubmed Central PMCID: 3155159.
64. Yuan J, Matsuura E, Higuchi Y, et al. Hereditary sensory and autonomic neuropathy type IID caused by an SCN9A mutation. Neurology 2013;80(18):1641–9. PubMed PMID: 23596073.
65. Axelrod FB. Familial dysautonomia. Muscle Nerve 2004;29(3):352–63. PubMed PMID: 14981733.
66. Slaugenhaupt SA, Blumenfeld A, Gill SP, et al. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet 2001;68(3):598–605. PubMed PMID: 11179008. Epub 2001/02/17. eng.
67. Mezey E, Parmalee A, Szalayova I, et al. Of splice and men: what does the distribution of IKAP mRNA in the rat tell us about the pathogenesis of familial dysautonomia? Brain Res 2003;983(1–2):209–14. PubMed PMID: 12914982. Epub 2003/08/14. eng.
68. Mendoza-Santiesteban CE, Hedges Iii TR, Norcliffe-Kaufmann L, et al. Selective retinal ganglion cell loss in familial dysautonomia. J Neurol 2014;261(4):702–9. PubMed PMID: 24487827.
69. Macefield VG, Norcliffe-Kaufmann LJ, Axelrod FB, et al. Relationship between proprioception at the knee joint and gait ataxia in HSAN III. Mov Disord 2013;28(6):823–7. PubMed PMID: 23681701. Pubmed Central PMCID: 3694996.
70. Palma JA, Norcliffe-Kaufmann L, Axelrod F, et al. Increased Frequency of Rhabdomyolysis in Familial Dysautonomia. American Academy of Neurology 2014;Abstract.
71. Freedman AM, Helme W, Havel J, et al. Psychiatric aspects of familial dysautonomia. Am J Orthopsychiatry 1957;27(1):96–106. PubMed PMID: 13402874. Epub 1957/01/01. eng.
72. Palma JA, Norcliffe-Kaufmann L, Fuente-Mora C, et al. Current treatments in familial dysautonomia. Expert Opin Pharmacother 2014;15(18):2653–71. PubMed PMID: 25323828. Pubmed Central PMCID: 4236240.
73. Indo Y. Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Hum Mutat 2001;18(6):462–71. PubMed PMID: 11748840. Epub 2001/12/19. eng.
74. Kaplan DR, Hempstead BL, Martin-Zanca D, et al. The trk proto-oncogene product: a signal transducing receptor for nerve growth factor. Science 1991;252(5005):554–8. PubMed PMID: 1850549. Epub 1991/04/26. eng.
75. Pinsky L, DiGeorge AM. Congenital familial sensory neuropathy with anhidrosis. J Pediatr 1966;68(1):1–13. PubMed PMID: 4158991. Epub 1966/01/01. eng.
76. Norcliffe-Kaufmann L, Katz SD, Axelrod F, et al. Norepinephrine deficiency with normal blood pressure control in congenital insensitivity to pain with anhidrosis. Ann Neurol 2015;Jan 27, PubMed PMID: 25627679.
77. Einarsdottir E, Carlsson A, Minde J, et al. A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. Hum Mol Genet 2004;13(8):799–805. PubMed PMID: 14976160.
78. Carvalho OP, Thornton GK, Hertecant J, et al. A novel NGF mutation clarifies the molecular mechanism and extends the phenotypic spectrum of the HSAN5 neuropathy. J Med Genet 2011;48(2):131–5. PubMed PMID: 20978020. Pubmed Central PMCID: 3030776.
79. Edvardson S, Cinnamon Y, Jalas C, et al. Hereditary sensory autonomic neuropathy caused by a mutation in dystonin. Ann Neurol 2012;71(4):569–72. PubMed PMID: 22522446.
80. Leipold E, Liebmann L, Korenke GC, et al. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. Nat Genet 2013;45(11):1399–404. PubMed PMID: 24036948.
81. Johnsen SD, Johnson PC, Stein SR. Familial sensory autonomic neuropathy with arthropathy in Navajo children. Neurology 1993;43(6):1120–5. PubMed PMID: 8170555.
82. Dagoneau N, Scheffer D, Huber C, et al. Null leukemia inhibitory factor receptor (LIFR) mutations in Stuve-Wiedemann/Schwartz-Jampel type 2 syndrome. Am J Hum Genet 2004;74(2):298–305. PubMed PMID: 14740318. Pubmed Central PMCID: 1181927.
83. Robertson D, Haile V, Perry SE, et al. Dopamine beta-hydroxylase deficiency. A genetic disorder of cardiovascular regulation. Hypertension 1991;18(1):1–8. PubMed PMID: 1677640.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324

84. Biaggioni I, Robertson D. Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency. Lancet 1987;2(8569):1170–2. PubMed PMID: 2890806.
85. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology 2010;75(1):64–71. PubMed PMID: 20505134.
86. Kaler SG. Inborn errors of copper metabolism. Handb Clin Neurol 2013;113:1745–54. PubMed PMID: 23622398. Pubmed Central PMCID: 4214864.
87. Donsante A, Sullivan P, Goldstein DS, et al. L-threo-dihydroxyphenylserine corrects neurochemical abnormalities in a Menkes disease mouse model. Ann Neurol 2013;73(2):259–65. PubMed PMID: 23224983. Pubmed Central PMCID: 3597755.
88. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology 1982;32(5):498–502. PubMed PMID: 6803189.
89. Pischik E, Kauppinen R. Neurological manifestations of acute intermittent porphyria. Cell Mol Biol (Noisy-Le-Grand) 2009; 55(1):72–83. PubMed PMID: 19268005.
90. Amiel J, Sproat-Emison E, Garcia-Barcelo M, et al. Hirschsprung disease, associated syndromes and genetics: a review. J Med Genet 2008;45(1):1–14. PubMed PMID: 17965226.
91. Hofstra RM, Valdenaire O, Arch E, et al. A loss-of-function mutation in the endothelin-converting enzyme 1 (ECE-1) associated with Hirschsprung disease, cardiac defects, and autonomic dysfunction. Am J Hum Genet 1999;64(1):304–8. PubMed PMID: 9915973. Pubmed Central PMCID: 1377732.
92. Weese-Mayer DE, Berry-Kravis EM, Zhou L, et al. Idiopathic congenital central hypoventilation syndrome: analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in PHOX2b. Am J Med Genet A 2003;123A(3):267–78. PubMed PMID: 14608649.
93. Weese-Mayer DE, Silvestri JM, Huffman AD, et al. Case/control family study of autonomic nervous system dysfunction in idiopathic congenital central hypoventilation syndrome. Am J Med Genet 2001;100(3):237–45. PubMed PMID: 11343310.
94. Chu ML, Berlin D, Axelrod FB. Allgrove syndrome: documenting cholinergic dysfunction by autonomic tests. J Pediatr 1996; 129(1):156–9. PubMed PMID: 8757578.
95. Koehler K, Malik M, Mahmood S, et al. Mutations in GMPPA cause a glycosylation disorder characterized by intellectual disability and autonomic dysfunction. Am J Hum Genet 2013; 93(4):727–34. PubMed PMID: 24035193. Pubmed Central PMCID: 3791256.
96. Spritzer SD, Zarkou S, Ireland SP, et al. Autonomic dysfunction in adult-onset alexander disease: a case report and review of the literature. Clin Auton Res 2013;23(6):333–8. PubMed PMID: 23925719.
97. DeStefano AL, Baldwin CT, Burzstyn M, et al. Autosomal dominant orthostatic hypotensive disorder maps to chromosome 18q. Am J Hum Genet 1998;63(5):1425–30. PubMed PMID: 9792870. Pubmed Central PMCID: 1377553.
98. Gonzalez-Duarte A, Norcliffe-Kaufmann L, Martinez J, et al. Cardiovascular and neuroendocrine features of Panayiotopoulos syndrome in three siblings. Epilepsy Behav 2011;21(3):296–300. PubMed PMID: 21474385.
99. Livingston JH, Cross JH, McLellan A, et al. A novel inherited mutation in the voltage sensor region of SCN1A is associated with Panayiotopoulos syndrome in siblings and generalized epilepsy with febrile seizures plus. J Child Neurol 2009;24(4):503–8. PubMed PMID: 19339291.
100. Hahn AF, Waaler PE, Kvistad PH, et al. Cold-induced sweating syndrome: CISS1 and CISS2: manifestations from infancy to adulthood. Four new cases. J Neurol Sci 2010;293(1–2):68–75. PubMed PMID: 20400119.

ISBN: 978-0-323-37101-8; PII: B978-0-323-37101-8.00324-6; Author: Swaiman & Ashwal & Ferriero & Schor & Finkel & Gropman & Pearl & Shevell; 00324