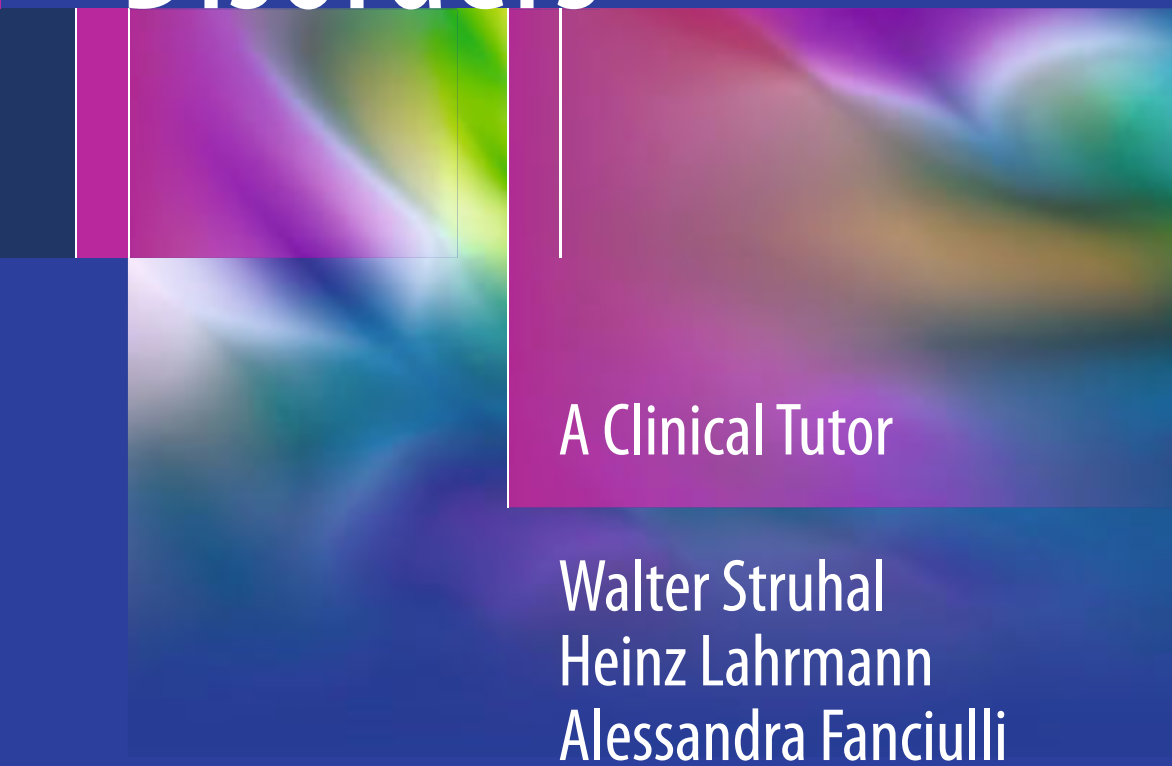
Bedside Approach to Autonomic Disorders



A Clinical Tutor

Walter Struhal
Heinz Lahrmann
Alessandra Fanciulli
Gregor K. Wenning
Editors

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Editors
Walter Struhal
Chair, Department of Neurology
Karl Landsteiner University
of Health Sciences
Site Tulln
Tulln
Austria

Heinz Lahrmann
Private Office
Vienna
Austria

Alessandra Fanciulli
Division of Clinical Neurobiology
Department of Neurology
Innsbruck Medical University
Innsbruck
Austria

Gregor K. Wenning
Division of Clinical Neurobiology
Department of Neurology
Innsbruck Medical University
Innsbruck
Austria

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General Approach to Patients with Autonomic Disorders: "What Is the Autonomic Disease?" – A Basic Tutorial to Autonomic Physiology and Pathophysiology

1

Heinz Lahrmann and Walter Struhal

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1.1 Introduction

Disorders of the autonomic nervous system (ANS) are often a severe burden to the quality of life of our patients (e.g., orthostatic intolerance, sweating disorders, sexual dysfunction). In some cases, they may be harmful (syncope with falls, heat intolerance, urinary retention) or even life threatening (sudden cardiac death, sympathetic storm, heat shock). Diagnosis of ANS disorders is still underrepresented,

H. Lahrmann, W. Struhal together with all co-authors.

H. Lahrmann (✉)
Private Office, 1030 Vienna, Austria
e-mail: NEUROLOGE@LAHRMANN.AT

W. Struhal
Chair, Department of Neurology, Karl Landsteiner University of Health Sciences, Site Tulln, Tulln, Austria
e-mail: walter.struhal@tulln.lknoe.at

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despite their common occurrence in clinical practice. This may be attributed at least in part to a lack of awareness and attention to symptoms of ANS dysfunction. Information on the ANS is rare in many neurological textbooks and often missing during education. This booklet shall help to recognize the presence and distribution of autonomic dysfunctions and provide tips for further management. The clinical investigations of autonomic functions presented here refer to the office, bedside, or prelaboratory evaluation. It cannot and shall not replace any textbook in this growing, neurological field.

ANS disorders may occur primarily (primary autonomic failure, multiple system atrophy (MSA)) or in the course of other diseases (Parkinson disease (PD), diabetes mellitus, stroke, Guillain-Barré syndrome (GBS)). They can be of central (preganglionic lesion in PD and MSA) or peripheral (postganglionic lesions in diabetes or GBS) origin. The anatomical and functional organization of the ANS is quite complex including structures within the brain, spinal cord, and peripheral nervous system with pathways permeating all organ systems (Fig. 1.1). Many feedback and feedforward loops are involved to control hemodynamics and vital functions (blood pressure (BP), heart rate (HR), ventilation, body temperature, blood gas allostasis, urogenital function) (e.g., see Fig. 1.2). To diagnose ANS disorders to the best starting point is to detect and test the most compromised functions. Thus, in many diseases involving the ANS, more than one diagnostic test will be needed. Diligent, symptom-guided history taking is the cornerstone in the autonomic evaluation and may spare the use of extensive testing in many patients (Chap. 2). The following aims of clinical ANS evaluation may be defined [4]: to recognize (1) the presence and distribution of autonomic dysfunction, (2) patterns of autonomic failure and its relation to specific syndromes, (3) treatable disorders, (4) further evaluation needed (e.g., autonomic laboratory), (5) time course, and (6) effect on patient. Following the results of this clinical examination of the patient with suspected autonomic disorder, further investigations may be planned, if necessary. A questionnaire-based survey revealed that cardiovascular and sudomotor tests are the most frequently used in European autonomic laboratories [1]. Some of these are integrated in modern commercially available EMG devices. However, results have to be interpreted with great care, particularly when comparing them to published normative values.

Many questions regarding cardiovascular regulation may be addressed using simple bedside tests, such as Schellong's orthostatic stress test [2]. If the results are not conclusive or more detailed information is needed, a set of standardized tests, the so-called Ewing battery [3], is available. The complexity of cardiovascular dynamics may be analyzed using simple or more sophisticated methods.

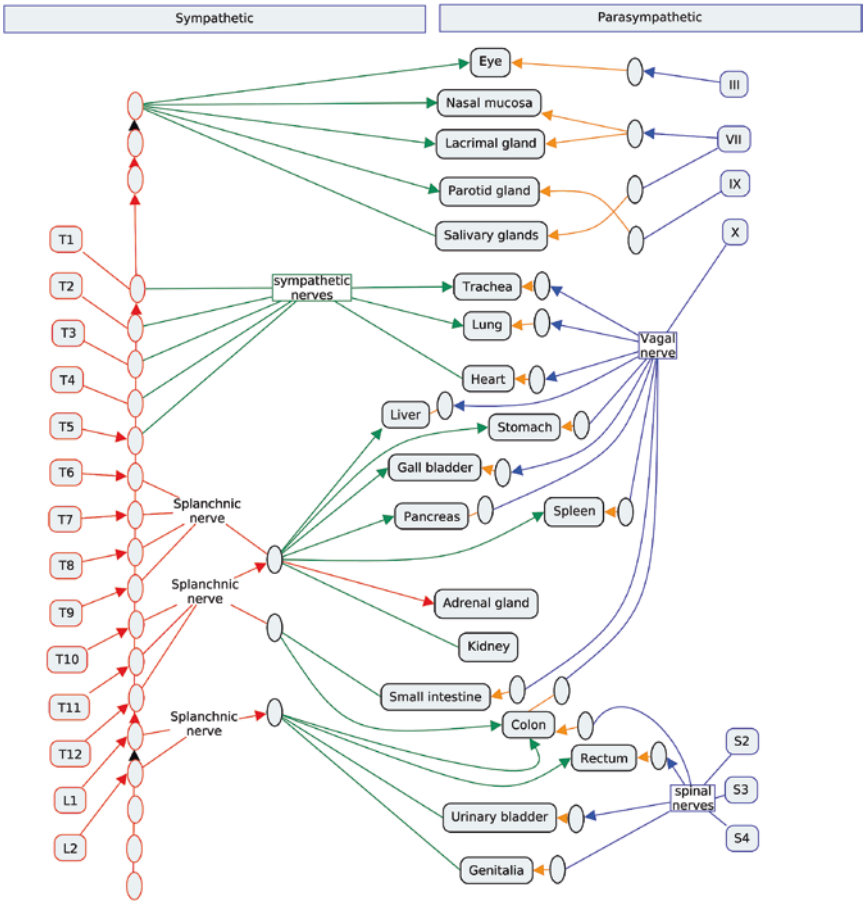

Fig. 1.1 Neuroanatomical organization of the ANS. Sympathetic preganglionic fibers (*red*). Sympathetic postganglionic fibers (*green*). Parasympathetic preganglionic fibers (*blue*). Parasympathetic postganglionic fibers (*yellow*)

1.2 Neuroanatomy

The ANS may be separated into a central and a peripheral part. The central autonomic network (CAN) is located mainly in the forebrain and brain stem (Table 1.1). These areas form a complex reciprocally interconnected network. Converging information is received from somatosensory and visceral input. This input is processed under the influence of behavioral state, sleep-wake cycle, mood, etc. Based

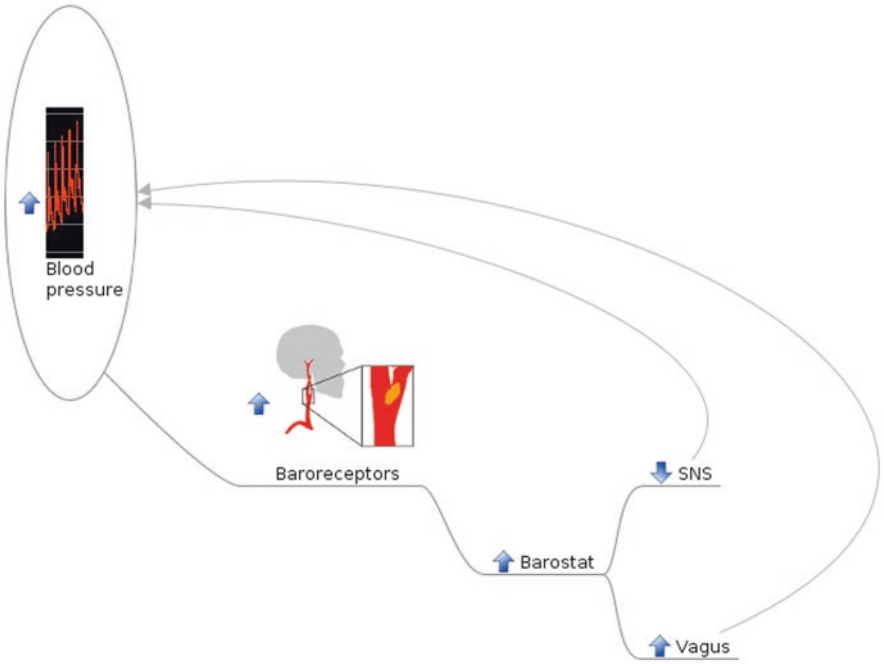

Fig. 1.2 Baroreflex. A negative feedback loop with two effectors, the baroreceptor reflex, controlling blood pressure by regulation of heart rate and blood vessel constriction. Baroreceptors detect BP increase and transmit afferent signals to the barostat in the brain stem, downregulating sympathetic innervation (SNS) (causing arterial vessel dilatation) and increasing parasympathethic (vagus) innervation (causing heart rate decrease). As a typical negative feedback loop, both the heart rate and the blood pressure in any normal subject show some degree of oscillation

on this processing, autonomic (sympathetic and parasympathetic neurons), motor (e.g., respiratory function via phrenic neurons), and endocrine (e.g., pituitary gland) outflow is generated. The hypothalamus is the highest level of autonomic integration, under the influence of cortical and limbic structures (Fig. 1.3). It maintains homeostasis and adapts and integrates individual needs such as hunger, thirst, sexual function, and sleep. The peripheral autonomic nervous system (pANS) is composed of the sympathetic and parasympathetic branch (Fig. 1.1). The enteric nervous system (ENS) is the most independent part of the ANS. It is located in the submucosal plexus of Meissner and the myenteric plexus of Auerbach. It controls gastrointestinal function (peristalsis and secretion) from the pharyngoesophageal junction to the anal sphincter. Input comes from the brain stem via sympathetic and parasympathetic neurons and from approximately 30% sensory neurons within the gut.

Table 1.1 CAN

Insular cortex	Primary viscerosensory (interoceptive) cortex receiving pain and temperature information
Anterior cingulate cortex	Regulation of affective behavior, modulates bodily arousal
Amygdala	Emotional significance of sensory input, conditioned fear response
Hypothalamus	Homeostasis and adaptation: thermoregulation, osmoregulation, food intake, stress response, reproduction, sleep-wake cycle, feeding, reward response
Periaqueductal gray	Integration of autonomic, somatic and antinociceptive responses to stressors (e.g., pain)
Parabrachial nucleus	Relay center for converging visceral, nociceptive and thermoregulatory stimuli to the hypothalamus
Nucleus of the solitary tract	First relay station of taste and visceral afferents, central relay station for all medullary reflexes (cardiovascular, respiratory, and gastrointestinal)
Ventrolateral medulla	Vasomotor tone, cardiac function, respiration
Medullary raphe	Thermoregulation and respiratory chemosensitivity

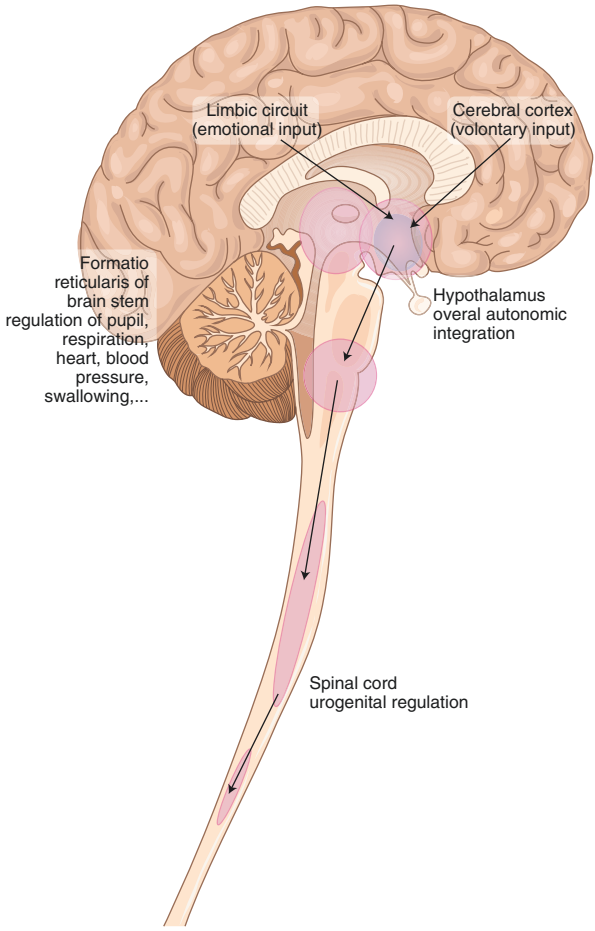

Fig. 1.3 The hypothalamus is the highest level of autonomic integration, under the influence of cortical and limbic structures

As *CAN* is described in detail in many exquisite textbooks on the ANS (e.g., Low et al.), we will only present a very short overview following E.E. Benarroch's description [5] to allow a basic understanding of the ANS necessary for clinical reasoning. Subsequently a special introduction to the gastrointestinal nervous system, to cardiocirculatory regulation, to control of sweating, and to sleep physiology will be given.

CAN includes the insular cortex, anterior cingulate cortex, amygdala, several nuclei of the hypothalamus, periaqueductal gray of the midbrain, parabrachial nucleus in the dorsolateral pons, and several medullary regions (nucleus of the solitary tract, ventrolateral reticular formation, raphe nuclei, dorsal vagal nucleus, nucleus ambiguus). CAN is hierarchically organized at all levels. The spinal level is the most caudal and constitutes the sympathetic segmental reflexes which are stimulus and target specific and the preganglionic parasympathetic neurons in the sacral spinal cord. More rostrally at the lower brain stem level, circulation, respiration, and micturition are controlled. At the upper brain stem level, autonomic control is integrated with pain and behavioral state. At the hypothalamic level, homeostasis is regulated. Forebrain structures control stress response and affective behavior, and the anterior limbic circuit integrates responses to emotions and behavior. In Table 1.1, the different structures of CAN and their functions are listed, as far as they are known. However, despite the hierarchical structure of CAN, its network architecture always has to be considered, particularly when interpreting cerebral images and lesions.

Transmission of excitatory signals within CAN is mediated by L-glutamate acting via AMPA, NMDA, and kainate receptors. Gamma-aminobutyric acid (GABA) is the main inhibitory transmitter acting via GABA-A and GABA-B receptors. The action of these fast-acting neurotransmitters is modulated by a variety of slower signals mediated by acetylcholine (ACh), monoamines, neuropeptides and neurosteroids, adenosine, and nitric oxide (NO), just to mention some of the most important ones.

Inputs to CAN comprise visceral afferent inputs (viscerоceptive information) and inputs from nociceptors, thermoreceptors, and muscle receptors. These signals are integrated at the different hierarchical levels of CAN. Dorsal horn neurons in lamina I represent the first line of integration and convey the information to higher regulatory centers (nucleus of the solitary tract, medullary network, thalamus, and insular cortex) (Fig. 1.5). There exists a viscerotopic representation in the insular cortex (viscerotopic homunculus). Other inputs to CAN originate from limbic and paralimbic areas and convey emotional information. Important humoral inputs are blood temperature, glucose level, osmolarity, and steroid hormones. Chemoreceptors in the ventral medulla react on changes in pCO_2 and pH and are involved in the control of respiratory and cardiovascular activity. O_2 level is controlled via receptors in carotid and aortic bodies.

Output is mediated by autonomic neurons, endocrine cells, and motor neurons (respiration, shivering, adaptive behavior). Autonomic outflow is mediated by preganglionic sympathetic and parasympathetic neurons. The *sympathetic* preganglionic neurons are located in the intermediolateral nucleus of T1–L3 levels of the spinal cord and are organized in functional units, each responsible for specific organ tasks. Preganglionic cholinergic neurons project via thin myelinated fibers to prevertebral and paravertebral ganglia. Postganglionic neurons use norepinephrine as transmitter except for cholinergic neurons innervating sweat glands. The *parasympathetic* output arises from preganglionic neurons within the brain stem and the sacral spinal

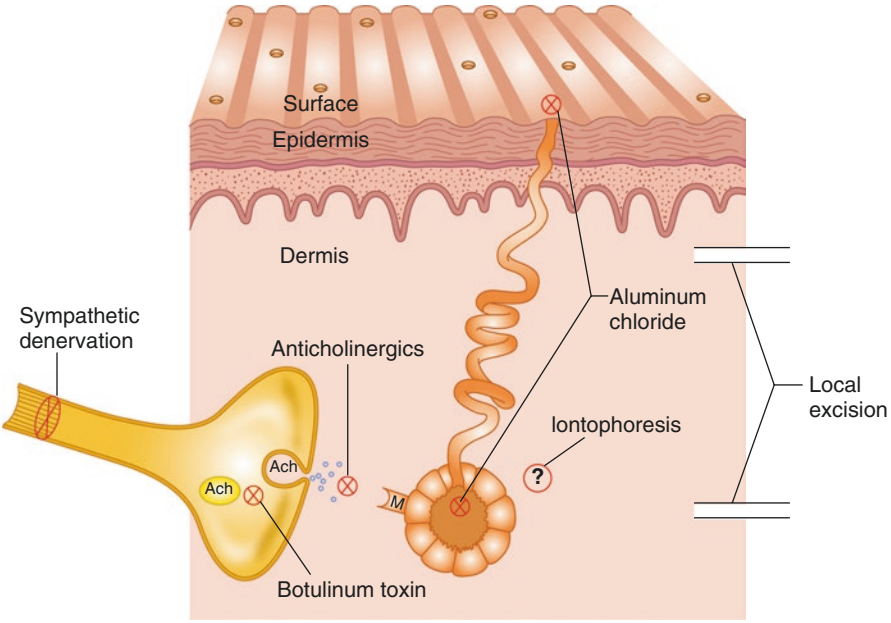

Fig. 1.4 A sympathetic sudomotor nerve and an eccrine sweat gland in glabrous skin. Included are the mechanisms of action of the therapeutic modalities for hyperhidrosis (see text). Surgical sympathetic denervation actually is performed more proximally, under video-assisted thoracoscopy, interrupting the corresponding extremity innervation along the thoracic sympathetic chain. The mechanism of action for iontophoresis is unknown. *ACh* acetylcholine; *M* muscarinic cholinergic receptor

cord. Most of the parasympathetic outflow is provided by the vagus nerve (dorsal nucleus and the ventrolateral portions of nucleus ambiguus) controlling the heart and respiratory and gastrointestinal function, the latter via the enteric nervous system except for the descending colon and rectum. The sacral preganglionic neurons are located in segments S2–S4 and are involved in the regulation of micturition, defecation, and sexual function. The so-called nucleus of Onuf at sacral levels S2–S3 innervates the external sphincters. All parasympathetic transmission is cholinergic and the preganglionic neurons synapse close to their target tissue.

The sympathetic neurotransmitter to the effector structures is norepinephrine, which acts via several subtypes of adrenergic receptors. Only sweat glands are innervated by acetylcholine (ACh). The primary neurotransmitter of the parasympathetic system is ACh. However, other mediators such as neuropeptides, NO, and ATP play an important role in the complex autonomic regulation.

1.2.1 Autonomic Cardiovascular Regulation

The cardiovascular system maintains appropriate supply of oxygen and nutrients to all organs and cells under continuously changing endogenous and exogenous demands. This is achieved globally by regulation of heart rate, blood pressure and

respiration during exercise, hypoxia, sleep, heat, and fever. At the local level, vasodilatation and contraction and endothelial permeability allow an adaptation to the demands of cells with increased metabolic activity (e.g., local infection, regeneration after injury). The global regulation is carried out by neural (brain stem, sympathetic and parasympathetic outflow) and humoral pathways. At organ and tissue level, regulation is achieved by local endothelial factors and autonomic reflexes (e.g., stretch reflex). Particularly blood pressure is regulated at a beat-per-beat basis to ensure an adequate perfusion of life-supporting organs. The most important and quite well-understood mechanism, the so-called arterial baroreceptor reflex, will be described in the following.

1.2.1.1 Arterial Baroreceptor Reflex, Fig. 1.2

The neuroanatomic components are the arterial baroreceptors (stretch-sensitive mechanoreceptors) in the adventitia of the carotid sinuses and aortic arch. They relay via myelinated (type A) and unmyelinated (type C) afferent fibers to the brain stem (nucleus tractus solitarius) and inhibit the vasomotor center. Finally, sympathetic outflow to the heart and blood vessels is decreased and parasympathetic outflow to the heart is increased. Thus, an increase in arterial blood pressure (ABP) with increased baroreceptor activity results in a reflectory decrease of blood pressure within the duration of one cardiac cycle. The baroreflex (BR) is continuously modulated, depending on the behavioral and physiologic conditions (exercise, sleep, emotions). This setting of the BR set point is achieved mainly by central activity.

The so-called baroreflex sensitivity (BRS) is commonly used to measure BR function. Techniques to quantify BRS include pharmacological methods using vasoactive drugs (Oxford method), the Valsalva maneuver, the neck chamber technique, and the analysis of spontaneous fluctuations of blood pressure and heart rate (sequence techniques) [6]. Any description of these tests would reach far beyond the scope of this booklet, and they cannot be used as "bedside tests" anyway.

1.2.1.2 Orthostasis and Active Standing

Standing up is a major challenge for the autonomic nervous system. Gravity acts on venous return and therefore reduces the blood flow reaching the central vains causing reduced central pressure. The reduced return of blood to the heart reduces the stroke volume (via Frank-Starling mechanism) and peripheral blood pressure. The baroreceptor corrects the reduction in blood pressure by increasing sympathetic and decreasing parasympathetic drive. Normal values for both methods are age dependent. According to EFNS guidelines, a fall in systolic pressure of at least 20 mmHg or in diastolic pressure of at least 10 mmHg within 3 min of standing or head-up tilt is considered to define orthostatic hypotension [7]. In MSA adapted criteria are applied (see Chap. 2). The head-up tilt test complements the autonomic evaluation of active standing up as it, conceptually, allows analyzing the hemodynamic modifications elicited by baroreceptor reflex activation without the interference of the muscular pump of the legs. Further, it should be performed in patients who cannot stand up actively and orthostatic dysregulation is highly suspected.

For history taking see Sect. 2.1.1, for clinical testing and management see Sect. 3.2.11

1.2.2 Autonomic Regulation of Sweating

Core body temperature is strictly maintained around 37 °C by the ANS, called the thermoneutral zone (TNZ). Heat production must exactly balance heat loss. Certain areas within the hypothalamus, periaqueductal gray, and medullary nucleus raphe pallidus form the autonomic network to control temperature. Input is derived from peripheral (skin cold and warm sensors) and central receptors (warm-sensitive (WS) neurons within the preoptic-anterior hypothalamus). Activity of WS neurons is affected by circadian rhythm, hormones (e.g., progesterone, prostaglandin E2), plasma cytokines, glucose levels, and osmolarity. Blood volume depletion (dehydration, blood loss) resulting in hypotension increases the activity of WS neurons. This leads to a fall in body temperature. Effector systems may be divided into autonomic thermoregulation (heat production by shivering and non-shivering, mainly metabolic thermogenesis and heat dissipation by sympathetic-mediated sweating and vasomotor control) and behavioral thermoregulation (environmental control, physical activity). Sympathetic skin innervation provides cholinergic sudomotor control (heat dissipation) and noradrenergic vasoconstriction (heat conservation). Active vasodilation is in part mediated by nitric oxide.

Sweating is the most effective method of heat dissipation in humans. Postganglionic sympathetic fibers are distributed segmentally (Fig. 1.1) and innervate two to four million sweat glands. These can be divided into apocrine and eccrine glands, whereas the latter are responsible for thermoregulation. Sweat glands of palms and soles do not participate in heat dissipation. Sweat glands consist of a secretory coil located in the lower dermis and the duct to the skin surface. Sweat is hypotonic in relation to plasma due to reabsorption of sodium and chloride in the duct. Only during increased sweating (exercise, fever, heat stress) a significant ion loss may occur (Fig. 1.5).

Generalized hyperhidrosis is usually part of some other underlying condition, and focal primary hyperhidrosis is idiopathic with a peak in the second and third decade of life. Hypohidrosis is most often part of other autonomic disorders (central lesions, alpha-synucleinopathies, ANP in diabetes, GBS, etc.).

Sweating helps to reduce core body temperature when it rises above TNZ. This can happen because of environmental heat exposure or decreased heat dissipation (e.g., excessive clothing or bed coverings) or as a result of increased heat production (e.g., excessive muscular activity).

Sweating increases with increasing depths of nonrapid eye movement (NREM) sleep. It is reduced during rapid eye movement (REM) sleep in the absence of emotionally charged dreams despite increases in brain glucose metabolism, increased temperature in many parts of the brain, increased skin sympathetic activity, and increased heart rate.

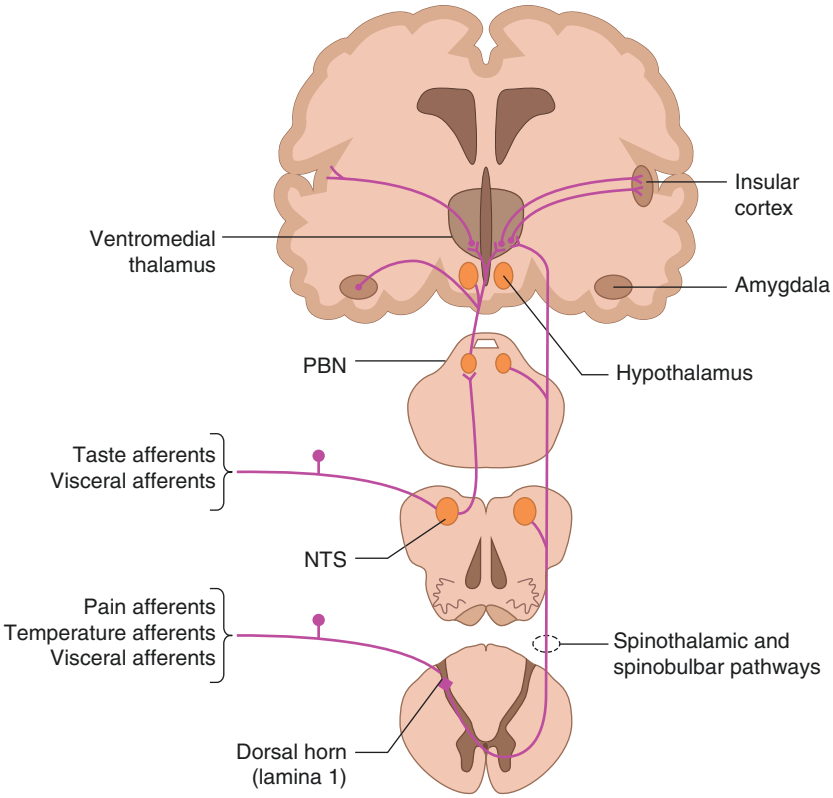

Fig. 1.5 Dorsal horn neurons in lamina I represent the first line of integration and convey the information to higher regulatory centers (nucleus of the solitary tract, medullary network, thalamus, and insular cortex). NTS: nucleus tractus solitarii; PBN: parabrachial nucleus

1.2.3 Autonomic Regulation of the Gastrointestinal Tract

Gastrointestinal functions are of immense importance for well-feeling and well-being. The gastrointestinal system therefore needs special attention when managing an autonomic patient. The gastrointestinal tract is innervated by an intrinsic and an extrinsic nervous system. The *intrinsic* or *enteric nervous system* (*ENS*) is located directly in the gut wall. It independently regulates the gastrointestinal function and is modulated by the extrinsic system constituted by the sympathetic and parasympathetic autonomic nerves (ANS) (Fig. 1.1).

The myenteric plexus (Auerbach's plexus) is situated between the circular and longitudinal muscle layers of the muscularis externa, and the submucosal plexus (Schabadasch and Meissner's plexus) is located under the mucosal layer (Fig. 6.1). The two plexuses modulate gastrointestinal motility through the interstitial cells of Cajal (ICCs), mesenchymal cells located between the plexus, which have contact

with each other or with smooth muscle cells. ICCs are thought to function as "pacemakers" generating slow waves in the smooth muscle layers of the gut and so accounting for spontaneous basic peristaltic movements [8]. ICCs are the target of excitatory impulses mediated by acetylcholine and substance P (SP) and inhibitory impulses mediated by vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) [9].

The ENS controls the gastrointestinal motility, predominantly in the small intestine, during the fasting state consisting of propulsive peristaltic anterograde movements, the so-called migrating motor complex (MMC). The MMC is important to keep the upper gastrointestinal tract free from food waste and to regulate the intestinal flora. The ENS also partially regulates the basic tonic contraction of the upper and lower esophageal sphincter, pylorus, and internal anal sphincter and the transient relaxation of the lower esophageal sphincter between meals.

With food intake, mechanical signals due to distension, as well as chemical signals, stimulate the ENS to generate reflexively inhibitory or excitatory modulation of the basic gastrointestinal activity independent from central and peripheral autonomic innervation [10].

The ENS controls the gastrointestinal motor activity and also modulates mucosal circulation and targets the neuroendocrine and immunological gastrointestinal cells. Mucosal blood microcirculation vessels play a crucial role in the absorption of nutrients and, together with neuroendocrine and immunological gastrointestinal cells, in the modulation of endocrine, immunological, and inflammatory activity of the gastrointestinal tract.

The *extrinsic nervous system* modulates the enteric functions and connects the ENS with the central nervous system (CNS). The CNS receives viscerosensory afferences from chemoreceptors and mechanoreceptors through sensory nerves and initiates regulatory reflexes (cranial and spinal) through autonomic sympathetic and parasympathetic pathways (Fig. 1.5).

The cranial parasympathetic autonomic innervation of the stomach and upper intestine is constituted by the vagus nerve (X cranial nerve), which comprises about 80–90% of sensory fibers whose cell bodies are located in the nodose ganglion (inferior ganglion of the vagus nerve). The afferent fibers terminate in the nucleus of the solitary tract in the medulla, which projects to higher brain regions, such as the hypothalamus and amygdala. The dorsal nucleus of the vagus nerve in the medulla sends efferent projections to the local ganglia of gastrointestinal tract. The right vagus nerve descends to the esophagus, contributes to the esophageal plexus, and enters the abdomen through the diaphragm as the posterior vagal trunk. The left vagus nerve after contributing to the esophageal plexus descends to the abdomen as the anterior vagal trunk. The vagus nerve is connected directly with the myenteric plexus of the stomach and controls gastric motility and emptying.

The spinal autonomic system is constituted by the splanchnic (sympathetic) and pelvic (parasympathetic) nerves (Fig. 1.1). Afferent fibers of those nerves have their cell bodies in the dorsal root ganglia. Efferent fibers to the splanchnic nerve (thoracic, lumbal, sacral) arise from the sympathetic trunk (T1–L2) in the intermediolateral cell

column and, after synapsing at the celiac, superior mesenteric, and inferior mesenteric ganglia, enter the celiac, intermesenteric, and hypogastric plexus. The pelvic nerve originates from the lateral gray matter of the sacral spinal cord (S2–S4) and enters the sacral plexus (inferior hypogastric plexus). The sympathetic gastrointestinal innervation is responsible for the vasomotor tone and the redistribution of regional blood flow during stress, exercise, temperature, and postural change. The parasympathetic gastrointestinal autonomic system modulates several reflexes important for gastrointestinal motility, sphincter control, and secretion.

Several CAN structures are involved in gastrointestinal autonomic innervation (Table 1.1). Forebrain regions including amygdala, hypothalamus, and insular and anterior cingulate cortex modulate autonomic function being in charge for emotions, stress, arousal, and endocrine responses as well as for visceral sensations. Some pontomesencephalic brain stem regions, such as periaqueductal gray and parabrachial area, are also important for integration of autonomic function with pain and stress connecting lower brain stem and spinal autonomic centers with the forebrain regions [11] (Fig. 1.5).

1.2.4 Modulation of Autonomic Control During Sleep

The *sleep-wake cycle* results from a rhythmic alternation and the inhibitory interactions of two contrasting systems: the arousal or activating system (cholinergic, serotonergic, and histaminergic nuclear groups of the rostral pons, midbrain, and posterior hypothalamus plus cholinergic neurons in the basal forebrain) and the anti-arousal or deactivating systems (medial preoptic-anterior hypothalamic region and adjacent basal forebrain and medial thalamus and medulla). These two systems act as a kind of flip-flop switch allowing the transition from wake to sleep states and vice versa. Orexin (hypocretin) stabilizes the system in one of the two states of vigilance [12]. This neuropeptide is synthesized in the perifornical and lateral regions of the hypothalamus and plays a key role in arousal, energy homeostasis, feeding, thermoregulation, and neuroendocrine and cardiovascular control.

A normal sleep period in an adult human is characterized by a cyclic alternation of two entirely different behavioral states: REM (rapid eye movement) sleep and non-REM (NREM) sleep. Additionally, NREM sleep is further divided into progressively deeper stages of sleep: stage 1 NREM, stage 2 NREM, and stage 3 NREM (deep or delta-wave sleep) [13].

REM sleep has tonic component characterized by electrocortical desynchronization and muscle atonia and phasic component characterized by the appearance of rapid eye movements and muscle twitches. The transitions between the different sleep stages are accompanied by changes in the control of the cardiovascular and respiratory system [14].

During nonrapid eye movement (NREM) sleep, the sympathetic control of the *cardiovascular* system decreases progressively and the parasympathetic tone becomes predominant. A marked reduction in blood pressure (BP) and heart rate (HR) occurs, becoming more pronounced as sleep progresses from stage 1 NREM to stage 3 NREM.

During REM sleep, the cardiovascular regulation becomes unstable. Surges of sympathetic activity, HR, and BP occur during phasic REM sleep.

During tonic REM sleep, a marked bradycardia and decreased peripheral resistance are observed and result in BP decrease below the levels reached in NREM sleep. This BP decrease is interrupted during bursts of rapid eye movements and muscle twitches by large transient increases in BP and HR which are the consequence of phasic inhibition of parasympathetic and phasic increase of sympathetic activity.

In the same way, the baroreceptor reflex, the most important mechanism for beat-to-beat control of arterial blood pressure (ABP), is variably modulated by central influences during the different sleep phases.

During NREM sleep, the baroreflex holds HR low despite decreasing BP, suggesting an increased baroreflex sensitivity. During REM sleep, the baroreflex responds differently to hypertensive or hypotensive stimuli.

Cardiovascular activity is further regulated by the arterial chemoreceptors in the carotid bodies. Hypoxia-induced stimulation of these chemoreceptors may lead to sympathetically mediated vasoconstriction resulting in a BP increase and vagally mediated HR decrease. This respiratory-cardiovascular interaction may be involved in the pathophysiology of harmful cardiovascular consequences like hypertension in OSAS [15].

In physiological conditions, healthy adults show a BP decline during sleep of 10–20% compared to mean daytime values. The fall in BP during the sleep period is referred to as a "dipping BP profile," its occurrence being considered important for cardiovascular health, as it is thought to provide what has been referred to as a "cardiovascular holiday". Important additional influences of sleep on cardiovascular functions may be exerted through variation in respiration [16].

Changes in *ventilation* also occur during sleep as breathing control is different during wake and NREM and REM sleep. In the transition from wakefulness to sleep, a progressive inactivation of voluntary control of ventilation is observed. NREM sleep ventilation is automatically controlled by chemical feedback related to CO_2 and O_2 levels. During sleep onset and light NREM sleep, breathing is characterized by oscillations in amplitude with only sporadic central apneas, while during deeper stages of NREM sleep, breathing becomes progressively regular. In this stage, a reduction in minute ventilation is observed due to a decrease in tidal volume and respiratory frequency. In REM sleep, breathing becomes irregular and central apneas or hypopneas of a few seconds occur sporadically, often in association with bursts of REMs. Alveolar ventilation decreases by 0.4–1.5 l/min, and pulmonary arterial pressure rises by 4–5 mmHg; nonetheless, these variables remain within the normal range.

Take Home Messages

- The autonomic nervous system is hierachically organized at all levels.
- The autonomic nervous system consists of the central autonomic network and the peripheral branches, sympathetic and parasympathetic
- The autonomic nervous system controls homeostasis of the whole body including cardiovascular activity, digestions, sexual function, sweating, and sleep.

References

1. Lahrmann H, Magnifico F, Haensch CA, Cortelli P (2005) Autonomic nervous system laboratories: a European survey. Eur J Neurol 12:375–379
2. Winker R, Prager W, Haider A, Salameh B, Rudiger HW (2005) Schellong test in orthostatic dysregulation: a comparison with tilt-table testing. Wien Klin Wochenschr 117:36–41
3. Ewing DJ, Clarke BF (1982) Diagnosis and management of diabetic autonomic neuropathy. Br Med J 285:916–918
4. Low PA, Sandroni P, Benarroch EE (2008) Clinical autonomic disorders: classification and clinical evaluation. In: Low PA, Benarroch EE (eds) Clinical autonomic disorders, 3rd edn. Wolters Kluwer, Philadelphia, pp 1–17
5. Benarroch EE (1993) The central autonomic network: functional organization dysfunction, and perspective. Mayo Clin Proc 68(10):988–1001
6. Struhal W, Hoedl S, Lahrmann H, Toeglhofer E, Gruber F, Vosko M, Ransmayr G (2011) Reliability of the noninvasive sequence methods to estimate baroreflex function using the paradigm of brain death. Auton Neurosci 161(1–2):43–45
7. Lahrmann H et al (2006) EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 13:930–936
8. Ward SM, Sanders KM (2006) Involvement of intramuscular interstitial cells of Cajal in neuroeffector transmission in the gastrointestinal tract. J Physiol 576(Pt 3):675–682
9. Olsson C, Holmgren S (2001) The control of gut motility. Comp Biochem Physiol 128:481–503
10. Altaf MA, Sood MR (2008) The nervous system and gastrointestinal function. Developmental disabilities research reviews 14:87–95
11. Drake MJ, Fowler CJ, Griffiths D, Mayer E, Paton JF, Birder L. Neural control of the lower urinary and gastrointestinal tracts: supraspinal CNS mechanisms. Neurourol Urodyn. 2010;29(1):119–27.
12. Grimaldi D, Silvani A, Benarroch EE, Cortelli P (2014) Orexin/hypocretin system and autonomic control: new insights and clinical correlations. Neurology 82:271–278
13. American Academy of Sleep Medicine (AASM) (2014) The international classification of sleep disorders, 3rd edn. American Academy of Sleep Medicine, Darien, IL, 2014.
14. Boudreau P, Yeh WH, Dumont GA, Boivin DB (2013) Circadian variation of heart rate variability across sleep stages. Sleep 36(12):1919–1928. doi:10.5665/sleep.3230
15. Task Force of the American Academy of Sleep Medicine (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 5(3):263–276
16. Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N (2013) Heart rate variability in normal and pathological sleep. Front Physiol 4:294. doi:10.3389/fphys.2013.00294

Autonomic History Taking and Key Symptoms: Where Is the Autonomic Disease?

2

Alessandra Fanciulli, Elisabetta Indelicato, and Gregor K. Wenning

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A. Fanciulli (✉) • G.K. Wenning
Division of Clinical Neurobiology, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
e-mail: alessandra.fanciulli@i-med.ac.at

E. Indelicato
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

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2.1 History Taking: You Need to Know What You're Looking for

The autonomic nervous system controls the cardiovascular, gastrointestinal, urogenital, respiratory, thermoregulatory, and pupillary function and regulates sleep. Such a wide distribution is reflected by the protean manifestations of autonomic disorders, which range from generalized failure to isolated organ dysfunction, thus mimicking, among others, primary disorders of the innervated organs.

Loss of function as well as hypo-, hyper-, or deregulated activation may turn into autonomic symptoms. The clinical course may be likewise variable, from a paroxysmal or acute onset to subacute or chronic evolution. Comorbidities and other non-autonomic etiologies need to be taken into account as well. Clinical assessment of patients with suspected autonomic disorders therefore relies on a holistic approach to the patient, combined with a targeted autonomic history taking.

The present chapter is divided into three sections:

1. Typical symptoms of each autonomic domain will be discussed together with possible causes and alternative, non-autonomic etiologies.
2. Other important aspects to be considered: age, gender, time course, family history, and comorbidities.
3. How to transfer symptoms into a feasible diagnostic hypothesis.

2.2 Key Autonomic Symptoms (Per Domain)

2.2.1 Cardiovascular Autonomic Dysfunction

2.2.1.1 How Does the Patient Complain About It

The key feature of cardiovascular autonomic impairment is "orthostatic intolerance," eventually resulting in syncope. Syncope is defined as a transient, self-limited, loss of consciousness, which occurs when global cerebral perfusion is impaired [54].

The most frequent cause of syncope is vasovagal (reflex) syncope that is induced by a paroxysmal, abnormal cardiovagal outflow, coupled with sympathetic inhibition in otherwise healthy subjects, which results in cardioinhibition, vasodepression, or, more frequently, a combination of both. In vasovagal syncope, loss of consciousness is heralded by a 30–60s-lasting presyncopal phase in which signs of autonomic arousal and of cerebral and retinal hypoperfusion occur. In this premonitory phase, autonomic activation may cause warm feeling, cold sweat, yawning, drooling, abdominal discomfort, nausea, cramps, or the desire to sit down or leave the room [63]. If the subject reacts at this stage by sitting or lying down, onset of syncope can be prevented. Otherwise, symptoms of cerebral and retinal hypoperfusion like light-headedness, fatigue, blurred vision, graying out of colors, tinnitus, or palpitation develop. If cerebral perfusion remains under the critical level (below 60 mmHg) for longer than 7 s, the cerebral ischemic anoxia reserve is overruled,

and loss of consciousness develops. Immediately before syncope occurs, subjects may turn pale and show pupil dilatation and inability to move. During syncope, postural tone is lost, and eyes are open: upward turning of the eyes, preceded by downbeat nystagmus, may occur. Loss of consciousness in syncope usually lasts 10–20s, but duration may be longer if cardioinhibition with prolonged asystole (up to 70s) develops. In this case, arrhythmic myoclonic jerks and loss of urine may be observed, whereas fecal incontinence is rare. Tongue biting, especially if sided, is also unusual in syncope and is rather indicative of seizures [54]. Immediately after cessation of syncope, flushing may occur, as well as moaning or growling. Recovery is typically quick in syncope (minutes), although fatigue, retrograde amnesia, sleepiness, or, to the contrary, euphoria or agitation may persist longer, especially in elderly patients.

Common triggers of vasovagal syncope are represented by prolonged standing position, warm ambient temperature, pain, vision of blood, needle phobia, or intense emotions. Autonomic activation may be also triggered by specific stimuli which originate in the gastrointestinal (swallowing, rectal examination, defecation), urogenital (micturition), or respiratory (cough, sneezing) tract, leading to a so-called situational syncope. Reflex vasovagal syncope may, rarely, have an atypical presentation, i.e., without the abovementioned prodroma. These are, in general, reported more frequently by female and younger subjects, probably due to more severe autonomic activation in the presyncopal phase, while older subjects may fail to recall premonitory symptoms, since they are more susceptible to retrograde amnesia.

Syncope occurring in aging individuals during neck manipulation or even upon mild stimuli such as head turning is suggestive of carotid sinus syndrome, that is, syncope associated with asystole >3 s or systolic blood pressure drop >50 mmHg upon carotid sinus stimulation, and should prompt further investigations, including carotid sinus massage [54].

Orthostatic hypotension (OH) is defined as an orthostatic blood pressure fall >20 mmHg systolic or >10 mmHg diastolic within 3 min of head-up tilt or standing [17]. It may also manifest with syncope, but since blood pressure fall is progressive and not abrupt in this case, patients more frequently complain of prolonged symptoms of cerebral and/or generalized hypoperfusion, including light-headedness, dizziness, fatigue, nausea, and cognitive slowing upon standing. Visual problems ranging from blurring to tunnel vision are also a common complaint, as well as, more rarely, scotomas and visual hallucinations due to occipital hypoperfusion [63]. Hypoperfusion in shoulder and neck muscles may result in head and neck pain with a characteristic “coat hanger” distribution. Altered blood supply may also trigger orthostatic dyspnea and angina in the absence of pulmonary and coronary artery disease. OH symptoms are typically alleviated by sitting or recumbent position and are exacerbated in the morning, after large meals, or with heat exposure [16].

If OH develops in the context of a primary autonomic disease (i.e., due to neurodegeneration of the ANS, like in α-synucleinopathies), this may be accompanied by supine and nocturnal hypertension in 30–50% of the patients [9, 11, 24]. Supine hypertension is mostly asymptomatic or manifests with supine headache, angina, or nocturia, but is important to be recognized, since pharmacological

interventions for OH may exacerbate hypertensive crises and cause end-organ damage on the long term [10].

A peculiar form of OH is delayed OH, that is, OH manifesting during prolonged standing (i.e., after 3 min of orthostatic challenge). Delayed OH is not uncommon in the elderly, otherwise healthy, population: it presents with OH-typical symptoms after prolonged standing or walking and may trigger syncope due to reflex bradycardia. Recent studies suggest that delayed OH may otherwise represent a milder, initial form of classical OH, especially if associated with parkinsonism or diabetes [21, 42].

Initial OH is characterized by a transient blood pressure decrease immediately on standing >40 mmHg systolic and/or >20 mmHg diastolic. Afterwards blood pressure quickly normalizes, so that duration of presyncopal symptoms is short (<30 s), but may still cause syncope in some occasions (e.g., during heat exposure) [17].

Finally, palpitations, anxiety, panic attacks, chest discomfort, dyspnea, and migraine-like headache are typical symptoms that may be reported by patients suffering from postural orthostatic tachycardia syndrome (POTS) [33], another syndrome of orthostatic intolerance, characterized by a disproportionate increase in heart rate in response to orthostatic stress (>30 bpm within 10 min of standing with respect to baseline or standing heart rate >120 bpm), whereas little or no change in blood pressure occurs. A vasovagal reflex may superimpose in one third of patients, causing syncope or presyncope.

For physiology see Sect. 1.2.1, for clinical testing and management see Sect. 3.2.11

2.2.1.2 Can I Be Sure? Alternative Etiologies to Take into Account

Dizziness, fatigue, and neck pain are rather vague symptoms, but the occurrence with postural changes, followed by a prompt resolution with recumbency, is highly suggestive of orthostatic hypotension. In this clinical scenario, non-neurogenic causes of orthostatic intolerance should be ruled out. These include hypovolemia, as a consequence of diarrhea, emesis, or blood loss, among others, and use of drugs, such as diuretics, neuroleptics, antihypertensives, and other vasoactive agents. Adrenal insufficiency, systemic mastocitosis, and carcinoid syndrome are other less common causes of hypovolemia, either due to chronic volume depletion or vasodilation [16] (Table 2.1). In this case, simultaneous evaluation of blood pressure and heart rate during postural changes supports the diagnosis. Indeed, when hypovolemia occurs, the blood pressure drop upon standing is usually coupled with a compensatory increase in heart rate, which is usually blunted (<10 bpm) or absent in case of neurogenic OH.

Syncope is one cause of transient loss of consciousness (T-LOC), but other causes of T-LOC may represent a diagnostic challenge in clinical practice. Assessing the ultimate cause of syncope may also prove difficult. The diagnostic mainstay is a careful clinical history which should focus on triggers, e.g., sudden postural changes or prolonged standing, and warning symptoms. If an abrupt onset, without prodromal symptoms, is reported, cardiopulmonary causes of syncope should be promptly investigated. A variety of heart diseases such as tachy- or bradyarrhythmia, ischemia, and valvular or structural cardiopathy may manifest with syncope [3].

Table 2.1 Key autonomic symptoms per domain and alternative etiologies

Symptom	Alternative etiology
Cardiovascular	
Orthostatic intolerance: Symptoms due to cerebral, retinal, or global hypoperfusion: Light-headedness, unclear thinking Blurred vision, loss of peripheral and color vision, darkened vision Coat hanger or low-back pain Angina pectoris Symptoms due to autonomic activation (missing in neurogenic OH): Sweating Facial pallor Nausea Pupillary dilatation Palpitations Yawning Hyperventilation	Hypovolemia (diarrhea, recent infection, blood loss) Medications (diuretics, neuroleptics, antihypertensive drugs, vasoactive agents) Hyperthyroidism Adrenal insufficiency (rare) Systemic mastocytosis (rare) Carcinoid syndrome (rare)
Transient loss of consciousness (syncope)	Cardiac syncope Generalized seizure Psychogenic pseudosyncope Psychogenic non-epileptic seizure Mimicries: Hypoglycemia Intoxication Drop attacks Cataplexy
Dermatological	
Hypohidrosis, anhidrosis	Anticholinergic drugs BoNT treatment Hypothyroidism Autoimmune disorders (Sjogren's syndrome) Primary skin diseases Burns Radiations Congenital dysplasia of ectodermal-derived tissues (rare)
Hyperhidrosis	Alcohol/drug abstinence Hyperthyroidism Systemic infection Occult or manifest neoplasm
Vasomotor disturbances: Cold hands/feet with pallor or cyanosis Cutaneous flushing Peripheral edema	Venous insufficiency Peripheral artery disease Cardiac, liver, or renal insufficiency

(continued)

Table 2.1 (continued)

Symptom	Alternative etiology
Urogenital	
Disorders of the urinary storage phase: Nocturia Urinary frequency and urgency with or without incontinence	Infections Benign prostatic hypertrophy (men) Pelvic floor relaxation/prolapse (women) Pelvic surgery Radiation
Disorders of the urinary voiding phase: Incomplete bladder emptying Double voiding Hesitancy Interrupted or poor stream	Benign prostatic hypertrophy (men) Masses Pelvic surgery Radiation Cauda equina syndrome
Erectile dysfunction, ejaculation disorders (men)	Cardiovascular causes Drugs (neuroleptics, sympatholytics) Smoking Prolactinomas Thyroid disturbances Psychogenic erectile dysfunction
Poor vaginal lubrication, genital hyposensitivity (women)	Menopause Thyroid disturbances Prolactinomas Cardiovascular causes Psychogenic sexual dysfunction
Gastrointestinal	
Dry mouth	Anticholinergic drugs Sjogren's syndrome Head/neck surgery and/or radiotherapy
Drooling	Benzocaine-containing drugs (cough drops), neurologic disorders with altered neuromuscular control (stroke, myasthenia, motor neuron disease, parkinsonism)
Dysphagia, regurgitation	Neoplasm Systemic sclerosis
Gastroparesis	Medications (Ca^{2+} antagonists, tricyclic antidepressants) Neoplasm Mesenteric vascular insufficiency
Constipation and/or diarrhea	Thyroid disturbances Disorders of Ca^{2+} metabolism Chagas' disease Hirschsprung's disease Intestinal bacterial overgrowth
Respiratory	
Sleep-related breathing disorders	Idiopathic sleep-related breathing disorders
Symptoms due to vocal cord palsy: Stridor Dysphonia	Laryngeal masses Chronic laryngitis Thyroid goiter Acromegaly Chest neoplasm (entrapment of the recurrent laryngeal nerve) Iatrogenic lesion of the recurrent laryngeal nerve (post-thyroidectomy)

Table 2.1 (continued)

Symptom	Alternative etiology
Periodic inspiratory gasps Agonic respiratory pattern Respiratory insufficiency of "pump failure" type	
Ophthalmological	
Dry eye	Allergic conjunctivitis Contact lenses Sjogren's syndrome (CAVE: widespread autonomic failure has been reported in this disease) Incomplete eyelid closure (due to scars, exophthalmos, or facial nerve palsy) Vitamin A deficiency (rare)
Symptoms of impaired pupillary dilatation: Diminished nocturnal vision	Cataract Retinal disorders (e.g., diabetic retinopathy)
Symptoms of impaired pupil light reflex: Blurred vision Photophobia Involuntary eyelid closure	Cataract Corneal/vitreous pathology Following refractive surgery

It may be particularly difficult to rule out generalized seizures, since myoclonic jerks may appear also in the setting of syncope, especially in case of prolonged asystole due to cardioinhibitory vasovagal activation [57]. However, myoclonic jerks tend to be few in number and arrhythmic in syncope, while they may last over minutes and show rhythmicity in generalized epileptic seizures.

Psychogenic disorders, like psychogenic non-epileptic seizures or psychogenic pseudosyncope, should be also taken into consideration in the differential diagnosis, especially if psychiatric comorbidities or emotional triggers can be pointed out at history taking, duration of unconsciousness is exaggeratedly long (up to 60 min), frequency of syncopal episodes is high, and atypical features are observed during the episode (e.g., eyelid flatter, swallowing).

Metabolic causes, like hypoglycemia, or more rare causes and mimicries of T-LOC like drop attacks or cataplexy should be also taken into account in the case of atypical presentation.

In elderly patients, history taking may be unclear or misleading, and a fall, due to postural instability, with consequent concussion and loss of consciousness, may be mistaken for a syncopal event. On the other hand, in older patients, fragile or with polypharmacy, orthostatic hypotension is also a frequent, treatable, cause for unexplained falls to be excluded.

Exercise intolerance due to cardiac autonomic neuropathy results from reduced response in heart rate and blood pressure during the strains. In this context, pre-existing left ventricular systolic dysfunction and silent ischemic coronary disease are to be ruled out. In particular, patients suffering from diabetic neuropathy may experience painless cardiac ischemia, because of reduced pain sensitivity [58].

In patients diagnosed with POTS, clinical workup should rule out iatrogenic causes (newly prescribed antihypertensive drugs other than β-blockers; high-dose antidepressants, especially SNRI and TCA; neuroleptics), hyperthyroidism, anemia, or more rare causes, like pheochromocytoma, or the presence of accessory conduction pathways as in Wolff-Parkinson-White syndrome [19].

2.2.2 Dermatological (Sweating and Vasomotor Disorders)

2.2.2.1 How Does the Patient Complain About Them

Thermoregulatory and sweating dysfunctions are often encountered in the setting of autonomic disorders. Both hypo- and hyperhidrosis (reduced and increased sweat production, respectively) may occur with a variable distribution.

Patients may complain of hypohidrosis as reduced tolerance to heat exposure and skin dryness. If global anhidrosis occurs, the inability of dissipating heat may, in turn, lead to hyperthermia with potentially fatal consequence [6].

Hyperhidrosis may manifest as drenching sweat, if the whole body is affected, or as localized sweating in the axillae, palms, soles of feet, and face. Secretomotor dysfunction may also cause gustatory sweating, which is a pathological sweating in response to stimuli that usually activate salivation, such as eating or food aroma [15].

Seborrhea may be reported, but causes other than dysautonomia, e.g., endocrinological, may be more relevant in its pathogenesis [37].

Alterations in skin vasomotor control are responsible for altered venous return, which results in peripheral edema, cold hands/feet, and Raynaud-like phenomena, with blueish or blanched extremities. Inappropriate vasodilation may manifest as paroxysmal cutaneous flushes.

In complex regional pain syndrome (formerly known as reflex sympathetic dystrophy), regional sweating and vasomotor abnormalities may occur together with sensory deficits, dystonic postures, and myoclonic jerks, following traumatic limb injury or without an apparent cause [8].

2.2.2.2 Can I Be Sure? Alternative Etiologies to Take into Account

Hypohidrosis occurs as a common side effect of drugs with anticholinergic properties such as tricyclic antidepressants, oxybutynin, and botulinum toxin, the latter being the treatment of choice for local hyperhidrosis. Sweating disturbances may be also caused by a variety of conditions, from alcohol or drug withdrawal to thyroid dysfunction. Hyperthyroidism is usually characterized by excessive sweating, while a reduced thyroid function is responsible for hypohidrosis and reduced heat tolerance. Drenching sweats may be a common sign of hypercatabolic states linked to systemic infections or neoplasms. Sweat glands may be involved in the course of primary dermatological disorders, vasculitis (Sjogren's syndrome), or burns and radiation therapy, resulting in regional or global anhidrosis. Congenital dysplasia of ectodermal-derived tissues may be a fairly rare cause of anhidrosis in children [6].

2.2.3 Urogenital

2.2.3.1 How Does the Patient Complain About Them

Normal urinary function consists of a *storage phase*, in which the bladder detrusor is inactivated and activation of urethral sphincter muscles prevents urine leak, and a *voiding phase*, in which bladder detrusor contraction and urethral sphincter relaxation promote passing of urine. Both the storage and the voiding phase are under involuntary and voluntary control. Neurogenic disorders may result in a variable combination of detrusor overactivity or underactivity, with or without sphincter dysfunction [46, 60].

Impairment of the urinary storage phase results in nocturia, urinary frequency, and urgency, with or without incontinence.

Symptoms of voiding phase dysfunction are reported as feeling of incomplete bladder emptying and need for a double voiding, along with hesitancy and interrupted or poor stream. Since post-void urine residual volume increases in case of voiding impairment, retention and overflow incontinence may superimpose.

The abovementioned lower urinary tract symptoms usually worsen during the course of chronic autonomic disorders and may even shift, e.g., from a storage dysfunction to a voiding or mixed one over time [60]. Recurrent lower urinary tract infections, retrograde pyelonephritis, and eventually urosepsis are frequent complications of neurogenic bladder disturbances. In case of large post-void residual urine volume, hydronephrosis and bladder and kidney stones may also occur.

Sexual dysfunction frequently accompanies urological autonomic failure. Erectile dysfunction in men often remains undiagnosed, but it has been reported that isolated erectile dysfunction may precede urinary symptoms over years in atypical parkinsonian symptoms like multiple system atrophy, actually belonging to the earliest, though unspecific, premotor disease signs [14]. Ejaculatory disorders may also be reported, including premature or delayed ejaculation or complete absence of semen emission if retrograde ejaculation takes place. Women may complain either of genital hyposensitivity with anorgasmia or pain during sexual activity due to poor vaginal lubrication [39].

2.2.3.2 Can I Be Sure? Alternative Etiologies to Take into Account

Lower urinary tract symptoms are a frequent complaint in the aging population of both genders, resulting from structural to functional disorders of the pelvic district, and clinical manifestations may overlap with those of urogenital autonomic failure.

Laboratory tests to exclude urinary tract infections are mandatory in case of acute onset of lower urinary tract symptoms, especially if dysuria is present, since infection is the most common, reversible cause. On the other hand, when recurrent infections occur, an underlying urodynamic disturbance should be excluded.

The most common etiology for lower urinary tract symptoms in men is represented by benign prostatic hyperplasia, whose prevalence has an exponential rise from the sixth decade of life. Obstructive symptoms, like poor or interrupted stream with hesitancy, are the most frequent complaints, but frequency and urgency can

occur, as well as incomplete emptying and retention, in the case of superimposing atonic bladder [18].

In women, urinary symptoms may develop as a consequence of pelvic floor relaxation and prolapses, especially after multiple labors, or in the presence of pelvic masses and scars.

Major pelvic surgery or pelvic radiation may produce urogenital symptoms in both sexes.

Bladder dysfunction occurring together with low-back pain, saddlelike sensory deficit, and variable motor and sensory loss in the lower extremities, is highly suspicious for a cauda equina syndrome and should prompt further investigation to rule out caudal entrapment (vertebral disc prolapses, fractures, neoplasms).

Aging is accompanied by an exponential increase in sexual disturbances as a result of multiple pathophysiological mechanisms. Poor vaginal lubrication or pain during sexual intercourse in a postmenopausal woman may reflect genital atrophy due to the physiological reduction in hormone levels. Chronic diseases, medications, and atherosclerotic changes may underlie an erectile dysfunction in older men. Thyroid disorders, prolactinomas, and gonadic hormone deficiency may manifest with sexual dysfunction, among others. Classical cardiovascular risk factors like smoking, hypertension, and dyslipidemia are further risk factors for erectile dysfunction of vascular origin. Failure in both erection and ejaculation phases may also occur as a consequence of prostate surgery or radiotherapy. Retrograde ejaculation is a recognized side effect of many drugs, especially sympatholytic agents.

2.2.4 Gastrointestinal

2.2.4.1 How Does the Patient Complain About Them

Symptoms of gastrointestinal autonomic dysfunction may arise at every level of the gastrointestinal tract and are divided into symptoms of the upper and of the lower gastrointestinal tract. Autonomic dysfunction of the upper gastrointestinal tract may manifest with:

1. Xerostomia, which is a complaint of dry mouth, due to reduced saliva production.
2. Drooling, an excessive pooling of saliva that flows out of the mouth. Drooling is often reported by patients suffering from parkinsonian syndromes, but in this context, it is mainly related to impaired deglutition, and it can even coexist with xerostomia in up to 30% of the patients [5].
3. Delayed bolus transit in esophagus, which may manifest with regurgitation and dysphagia.
4. Delayed gastric emptying, presenting with bloating, belching, and early satiety. Gastroparesis may also cause nausea, postprandial vomiting, and anorexia.

Symptoms of the lower gastrointestinal tract may produce a variety of symptoms. Constipation and colic pain are by far the most reported. A long-standing constipation may, in turn, promote bacterial overgrowth, which results in

intermittent diarrhea. Apart from constipation, dissynergic contraction of pelvic muscles and anal sphincter may contribute to evacuation difficulties or to involuntary loss of stool [13]. Rarely, focal dystonia of the striated anal sphincter may result in refractory constipation [26].

2.2.4.2 Can I Be Sure? Alternative Etiologies to Take into Account

A detailed pharmacological anamnesis is the first step in the evaluation of salivary disturbances. Dry mouth is a common side effect of anticholinergic drugs, whereas benzocaine (contained in cough drops and over-the-counter medications for mouth ulcers) may cause sialorrhea. Xerostomia is a key feature of Sjögren's disease and associated connective tissue disorders. Dryness may involve also the eyes both in Sjogren's disease and autonomic failure. Reduced salivary production may follow surgery and radiotherapy for head and neck tumors. Drooling is frequently encountered in the setting of altered neuromuscular control of swallowing, such as bulbar form of amyotrophic lateral sclerosis, myasthenia gravis, or cerebral palsy.

Symptoms of chronic, delayed bolus transit may result from anatomical obstructions and should prompt exclusion of malignancies. Mesenteric vascular insufficiency should also be considered as a likely cause of gastroparesis in the elderly. Medications (Ca^{2+} blockers, antidepressants) and metabolic disturbances (hypothyroidism and hypercalcemia) should be excluded as common causes of chronic constipation. Rare etiologies for obstructive colonic symptoms are represented by Chagas' disease and Hirschsprung's disease, respectively, an infective and hereditary cause of enteric nervous system degeneration. Systemic sclerosis with visceral involvement may also be a rare case of gastrointestinal obstruction, especially at esophageal level.

2.2.5 Respiration and Sleep

2.2.5.1 How Does the Patient Complain About Them

Respiratory symptoms may be an early manifestation of autonomic failure in patients with multiple system atrophy (MSA), though commonly associated with advanced stages and, overall, constituting a poor prognostic predictor [25]. Obstructive sleep apnea is generally an early manifestation, while central sleep apnea may develop later on, when degeneration of brainstem breathing relays occurs [48]. Sleep-related breathing disorders are typically reported by the patient's bed partner, while the patient himself may be less aware of them. These include enhanced or new-onset snoring and stridor, a harsh and strained high-pitched inspiratory sound that occurs especially, but not only, at nighttime, which is due to pathological adduction of the vocal cords and is typically accompanied by chronic dysphonia. Sleep is not restorative in these patients, who also complain about sleepiness and sleep attacks during daytime.

In patients with severely impaired central respiratory drive, awake breathing rhythm alterations, like periodic inspiratory gasps or agonic respiratory patterns, may occur, as well as respiratory insufficiency of "pump failure" type [35].

2.2.5.2 Can I Be Sure? Alternative Etiologies to Take into Account

When sleep-related disorders precede other autonomic or motor manifestations, they cannot be distinguished from idiopathic sleep-related disordered breathing. Anecdotal reports of surgical intervention for snorers, who were eventually diagnosed with multiple system atrophy (MSA), underline the importance of a careful differential diagnosis [25].

Chronic stridor and other inspiratory disorders result from a partial obstruction of the upper respiratory tract, usually at glottic or supraglottic levels [38]. Clinical examination by the otorhinolaryngologist is required to exclude neoplastic, cystic, or inflammatory lesions of the larynx. Extrinsic stenosis may be caused by disorders of the adjacent structures, such as thyroid goiter or cancer, or result from neck surgery and radiotherapy. Soft tissue swelling secondary to acromegaly is a less common cause of obstruction and sleep apnea. Unilateral vocal cord palsy may be caused by chest or mediastinal neoplasm entrapping the recurrent laryngeal nerve or by accidental lesion of the recurrent laryngeal nerve during thyroid surgery.

2.2.6 Ophthalmological Autonomic Dysfunction

2.2.6.1 How Does the Patient Complain About It

Autonomic disorders may affect both lacrimation and pupillomotor function. Patients may complain of xerophthalmia, dry eyes, which results from impaired cholinergic stimulation of lacrimal glands.

Reduced nocturnal visual acuity and blurred vision, photophobia, and involuntary eyelid closure to light are typical symptoms of altered pupillomotor function due to impaired iris dilation and pupil light reflex, respectively [67]. Basal alterations of pupil diameter or altered pupillary response to cholinomimetic or sympathomimetic drugs are usually not noted by the patients [65].

2.2.6.2 Can I Be Sure? Alternative Etiologies to Take into Account

Eye dryness is a cardinal feature of Sjögren's disease. Autonomic failure is not frequent in Sjogren's disease, although cases with severe cardiovascular autonomic failure have been described [49]. Incomplete eyelid closure, e.g., after facial nerve palsy or previous injuries with scarring, is a mechanical cause of eye dryness to be excluded. Xerophthalmia is a classical manifestation of vitamin A deficiency, by now a rare finding in developed countries.

Diminished night vision is frequently reported as a consequence of cataract, typically in elderly subjects, but other causes include a variety of retinal disorders, like diabetic retinopathy, among others. Photophobia may occur in association with cataract and corneal or vitreous disturbances or as a side effect of refractive surgery.

2.2.7 Useful Screening Tools: Autonomic Questionnaires

Standardized questionnaires represent a useful tool to assess and rate the severity of autonomic symptoms. The most suitable one should be chosen among the validated

available scales on the basis of physician's purpose. The Composite Autonomic Symptom Scale (COMPASS) and the Composite Autonomic Scoring Scale (CASS) have been developed to introduce a scoring system of autonomic symptoms' severity and a correlation with autonomic function tests, respectively. The COMPASS is a self-administered survey, consisting of 84 items, and has been validated in a variety of autonomic disorders. A shorter version, the COMPASS-31, has been also developed [50].

The orthostatic hypotension questionnaire (OHQ) is a ten-item scale, purposely developed to assess severity of symptoms due to orthostatic hypotension and their impact on daily activity [27].

Specific questionnaires have been developed to evaluate autonomic symptoms in different diseases. The Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT), a self-administered, brief questionnaire which covers cardiovascular, gastrointestinal, urinary, thermoregulatory, pupillomotor, and sexual domains, is recommended for patients with Parkinson's disease [41]. The Unified Multiple System Atrophy Rating Scale (UMSARS) evaluates severity of motor and autonomic symptoms in patients with multiple system atrophy and can be used to monitor disease progression as well. Questions about disease-specific autonomic symptoms are included in UMSARS part I, a broader historical review, and results of quick orthostatic challenge test are reported in UMSARS part III [61].

2.3 Other Important Clues from History Taking

2.3.1 Time Course: Episodic/Situational, Acute, Subacute, and Chronic Symptoms

The mode of onset and the time course of autonomic symptoms provide essential clues for an etiological diagnosis. An episodic time course is, for example, typical of orthostatic and situational vasovagal syncope, where triggering or exacerbating factors can be pointed out at history taking. An acute or subacute onset of autonomic disturbances usually prompts to an immune etiology, such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute autonomic ganglionopathy, or a paraneoplastic syndrome. An AIDP, also known as Guillain-Barré syndrome, manifests with ascending flaccid paralysis and areflexia, frequently after an infectious illness. It has a monophasic evolution, usually without recurrence, and severe autonomic disturbances, such as arrhythmia and marked hypo- and hypertensive peaks, may occur in up to 20% of the patients during the disease course [68].

An acute monophasic time course, frequently followed by spontaneous remission or stabilization, as well as a premorbid report of infectious illnesses is suggestive of acute autonomic ganglionopathy, while in paraneoplastic syndromes, a subacute onset, often preceding the diagnosis of malignancies, is common.

Isolated attacks with generalized or organ-specific autonomic dysfunction may occur as a consequence of drug or toxin exposure, such as organophosphate pesticides. Autonomic crises are also a typical feature of some rare diseases with autonomic nerve involvement such as Riley-Day syndrome and porphyria.

A chronic, progressive course of autonomic symptoms points towards a degenerative pathology of the autonomic nervous system which may occur alone, as in pure autonomic failure, or in combination with additional neurological features as in MSA, Parkinson's disease, and dementia with Lewy bodies. Autonomic failure is typically progressive and ranges from milder manifestation in Parkinson's disease to severe dysautonomia in pure autonomic failure and multiple system atrophy [55].

2.3.2 Age and Gender

With the exception of vasovagal syncope, which may also occur in otherwise healthy children, disease onset in the childhood or teenage points toward a genetic cause.

In the age range from 10 to 30 years, up to 47% of the females and 31% of the males experience at least one syncopal episode, vasovagal syncope being by far the most common etiology. Syncope shows a second peak of incidence after the age of 65, with cardiopulmonary causes playing a key role in this age cluster [54].

POTS and vasovagal syncope show a striking female prevalence, usually affecting young women in childbearing age [19].

Primary forms of autonomic failure are characterized by a sporadic adult onset in the sixth or seventh decade [56, 62]. MSA and pure autonomic failure have a similar incidence in both genders, while Parkinson's disease has a 1.5 times higher male prevalence. Recent evidence suggests that some autonomic symptoms in Parkinson's disease may be more frequent and progredient in male patients [52]. In secondary autonomic failure, the gender prevalence and the age of onset depends on the underlying causative disease. Thus, like other autoimmune disorders, AAG may more frequently affect female patients in their young or middle adulthood, while diabetic and uremic neurogenic OH typically affect older individuals.

The presentation of autonomic disturbances itself may be also influenced by age. For instance, orthostatic intolerance more often features light-headedness in the young and cognitive slowing in the elderly [32].

2.3.3 Family History

Autonomic failure may occur in a number of rare genetic diseases including familial amyloidosis, Fabry disease, hereditary sensory autonomic neuropathies, and porphyrias [15]. The main presentation is a peripheral neuropathy with both autonomic and sensory deficits. Additional manifestations and familial recurrence pattern are helpful clues to address genetic testing.

Familial amyloidosis is an autosomal dominant inherited disease, caused by mutations in the gene coding for transthyretin. Like in acquired forms of amyloidosis, the aberrant form of transthyretin accumulates in different organs. Peripheral nerves are the second most common site of deposition after cardiovascular system, and this accounts for the frequent autonomic and sensitive neuropathic manifestations.

Fabry disease is due to an X-linked mutation in the enzyme α-galactosidase A that leads to lysosomal accumulation of glycosphingolipids. It manifests with early-onset heart failure, renal failure, and stroke. Neuropathic involvement results in painful crises and sweating disorders. According to its X-linked genetics, Fabry disease affects predominantly male patients, but heterozygous female carriers may also become symptomatic [44].

Hereditary sensory autonomic neuropathies (HSAN) are currently classified in five forms on the basis of the genetic substrate and clinical presentation. They usually feature mixed autonomic and sensory manifestations with the exception of HSAN III. This form, also known as Riley-Day syndrome or familial dysautonomia, shows a selective absence of unmyelinated fibers and manifests as isolated autonomic crises with onset in the childhood [40].

Isolated sympathetic noradrenergic failure is the unique manifestation of dopamine β-hydroxylase deficiency, a rare genetic disorder with autosomal recessive transmission [45]. It selectively impairs conversion of dopamine into noradrenaline in peripheral nerves; thus, parasympathetic and sympathetic cholinergic functions (sweating) are normally preserved. The usual presentation is a combination of orthostatic hypotension and eyelid ptosis in children.

2.3.4 Comorbidities: Main Suspects

In patient with polypharmacy, the first step is to review drug schedules for potential offending drugs, especially if recent changes have been applied. As mentioned before, high-dose antihypertensive or psychotropic drugs are the main cause of new-onset OH. Anticholinergic drugs, either for treatment of bladder detrusor overactivity or for symptomatic treatment of parkinsonism and dystonia, may in turn induce xerostomia, accommodation difficulties, gastrointestinal dysmotility, and atonic bladder.

Secondary involvement of ANS is far more common than primary autonomic disorders; thus, exclusion of metabolic or immunologic etiologies is a key step in the diagnostic workup.

Fasting blood glucose and glycated hemoglobin levels should always be checked as diabetes mellitus is a leading cause of autonomic neuropathy, and an altered glycemic control represents its strongest predictor [58]. Autonomic neuropathy may also arise in the setting of uremia, liver disorders, chemotherapy, neck or thoracic radiotherapy, and nutritional deficiencies.

A panel of immunological test may be performed to exclude autoimmune conditions with secondary dysautonomia, such as Sjögren's disease, rheumatoid arthritis, and systemic lupus erythematosus.

Borreliosis, leprosy, botulism, syphilis, and HIV infection may also present with autonomic neuropathy. Autonomic involvement during infectious illness may be a consequence of direct microbial neurotropism, neurotoxin production, or autoimmunity triggered by molecular mimicry. The latter is the likely mechanism which underlies post-infectious acute autoimmune demyelinating polyneuropathy.

Subacute onset of autonomic symptoms without other apparent causes in middle-aged individuals should rise suspicion for an occult neoplasm. Different mechanisms may account for ANS involvement in cancer, including direct infiltration, chemotherapy-related toxicity, nutritional alterations, or, in the absence of the previous, paraneoplastic manifestation [2] . Paraneoplastic autonomic syndromes frequently present together with sensory neuropathy. The autoantibody most commonly associated is anti-Hu; others are anti-PCA-2 and anti-CRMP-5 [16]. Small-cell lung cancer is present in more than 80% of the seropositive patients, but autonomic and sensory deficits may antedate the tumor diagnosis, which, when found, tends to be localized and treatment responsive. History taking should focus on suggestive features like tobacco consumption, nocturnal sweating, or unexplained weight loss, and a total body scan should be performed.

2.3.5 Additional Neurological Signs

Autonomic dysfunction may occur isolated or, more often, as a part of a disorder with a broader neurologic presentation. As mentioned above, sensory neuropathy accompanies autonomic failure in hereditary sensory autonomic neuropathies and, frequently, in paraneoplastic syndromes.

Diabetic peripheral neuropathy usually presents with a mixed autonomic and distal sensorimotor phenotype. Sweating and vasomotor abnormalities occur along with pain, numbness, paresthesia, areflexia, and weakness which spread from the extremities in a length-dependent fashion [4].

In neurodegenerative disorders of the central nervous system, autonomic failure is part of a complex presentation which may include parkinsonism, ataxia, pyramidal signs, and dementia. A combination of these features along with the severity of dysautonomia guides the differential diagnosis, which may be particularly difficult prior to develop a full-blown clinical picture (Fig. 2.1).

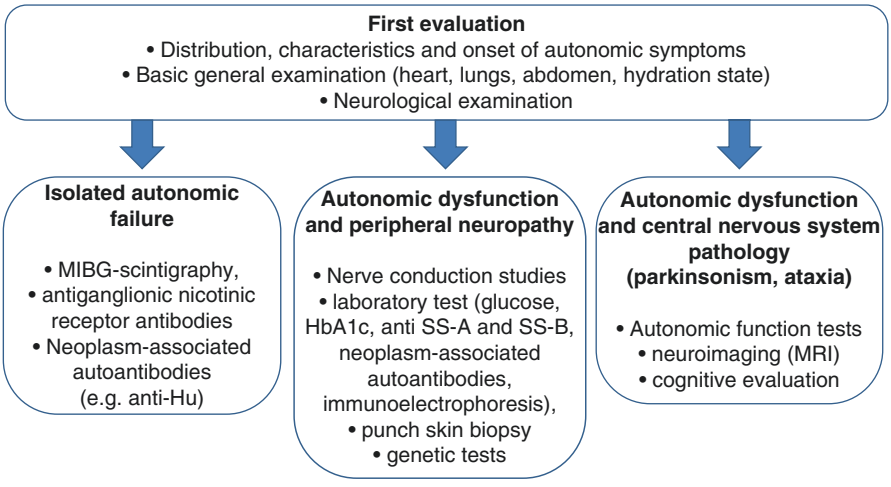

Fig. 2.1 Turning the jigsaw into an autonomic diagnostic hypothesis

2.4 From Autonomic Symptoms to a Diagnostic Hypothesis

2.4.1 Primary Autonomic Diseases

Autonomic failure is a key feature of a group of sporadic neurodegenerative disorders, whose pathological hallmark is represented by α-synuclein inclusions. α-synuclein accumulates within oligodendroglial cytoplasmic inclusion in MSA, and within neuronal cytoplasmic inclusions, the so-called Lewy bodies, in PD, dementia with Lewy bodies and pure autonomic failure. α-synuclein accumulates within oligodendroglial cytoplasmic inclusion in MSA and inside neuronal somas, Lewy bodies, or Lewy neurites, among others.

MSA is a progressive, fatal disorder which features parkinsonism, cerebellar and pyramidal symptoms, and autonomic failure in various combinations. Autonomic failure is an early and prominent manifestation which is underlain by a likewise conspicuous neurodegeneration over hypothalamus, noradrenergic and serotoninergic brainstem nuclei, and intermediolateral columns in the spinal cord [12].

A diagnosis of probable MSA requires the presence of urogenital dysautonomia (urinary incontinence plus erectile dysfunction in men) or an orthostatic fall by at least 30 mmHg in systolic or 15 mmHg in diastolic blood pressure within 3 min of standing or head-up tilt [23]. Further features of dysautonomia in MSA are represented by generalized hypo- or anhidrosis, stridor, and sleep-related breathing disturbances [31]. The association of these features with a poorly levodopa-responsive parkinsonism or a sporadic adult-onset cerebellar ataxia is highly suggestive of MSA.

The parkinsonian variant of MSA may be easily mistaken for idiopathic PD, especially at disease onset [31]. Autonomic failure in PD is milder and usually a later manifestation. Neuropathological changes involve both central autonomic nuclei and, to a greater extent, peripheral autonomic relays. Constipation is a common premotor manifestation of PD [1] and one of the most reported non-motor symptoms. A variety of urinary complaints, and particularly nocturia, may be present in up to 75% of the patients with PD [46]. Prevalence of OH is 30% in PD, ranging from 14% in drug-naïve patients to 52% in advanced stage of the disease [10].

Dementia with Lewy bodies is defined by the presence of progressive dementia with fluctuating cognition and parkinsonism [34]. The burden of autonomic dysfunction is considered intermediate between MSA and Parkinson's disease [55]. A high prevalence of carotid sinus hypersensitivity has been reported in patients with dementia with Lewy bodies [28].

Pure autonomic failure is a rare α-synucleinopathy which is defined by the presence of isolated autonomic disturbances, mainly severe OH, without additional neurological features. α-Synuclein mainly accumulates in peripheral autonomic nerves in pure autonomic failure [20]. Many cases of pure autonomic failure may develop parkinsonism or cognitive impairment during the disease course, eventually evolving into PD, MSA, or dementia with Lewy bodies. Pure autonomic failure is settled at the extremity of a spectrum in α-synuclein distribution pattern, since it selectively involves peripheral ANS and spares the central nervous system.

Autonomic failure has been also reported in τ-pathies like progressive supranuclear palsy and frontotemporal dementia.

Progressive supranuclear palsy is an atypical parkinsonism, characterized by poor L-dopa responsiveness, vertical gaze palsy, and frequent falls. Three years after disease onset, urinary urge or incontinence has been reported in 54% of the patients [7]. Occurrence of OH in progressive supranuclear palsy is debated, with some studies reporting similar prevalence of OH like in PD, but others not confirming this observation [29, 47].

The presence of cardiovascular autonomic failure was recently reported in patients with frontotemporal dementia, another τ-pathy characterized by severe cognitive impairment, behavioral abnormalities, and signs of first and second motor neuron degeneration in different combinations. In these patients, the presence of OH may remain underdiagnosed, due to inability of the patient to communicate symptoms [51].

A new entity, the cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS), has been recently described and is pointed as a further cause of autonomic dysfunction [64]. The presentation with cerebellar ataxia and autonomic symptoms may mislead to a diagnosis of MSA cerebellar variant, but the presence of a sensory neuronopathy such as a more benign course may be supportive. Both autonomic and sensory symptoms probably result from a degenerative ganglionopathy, as suggested by neuropathological studies [53].

2.4.2 Secondary Autonomic Diseases

A variety of systemic illnesses may affect the peripheral nervous system and produce autonomic symptoms. Chronic alcohol consumption, metabolic disorders, autoimmunity, or toxins are among the implicated factors.

One of the main causes of secondary autonomic dysfunction, as mentioned above, is represented by diabetes mellitus. Autonomic neuropathy is one of the multifaceted manifestations of peripheral nervous system involvement in diabetes, which also includes distal sensory motor neuropathy and mononeuropathies. Reports on prevalence and time onset are contrasting; even if autonomic neuropathy is usually a complication of a long-standing diabetes, it may appear within a year from the diagnosis in type 2 and within 2 years in type 1 diabetes patients [43]. Poor glycemic control seems to be crucial in its development [22, 69]. The manifestations may range from a global autonomic failure to an asymptomatic dysfunction which may be detected when autonomic tests are performed. When autonomic involvement appears in the context of a classical distal neuropathy, hypo- or anhidrosis and vasomotor disturbances develop together with sensory disturbances in the extremities. Visceral involvement manifests as gastroparesis, which may be particularly severe, alternating constipation and diarrhea, cystopathy, and erectile dysfunction [58]. Strict glucose

and glycated hemoglobin targets should be avoided in these patients, since loss of sympathetic activation during hypoglycemia may result in hypoglycemia unawareness and a higher risk of hypoglycemic coma. Cardiovascular autonomic neuropathy may also develop, carrying along a higher overall mortality and morbidity [59]. Symptoms of cardiovascular dysfunction in diabetes are represented by resting tachycardia, orthostatic hypotension, reduced tolerance to exercise, and painless myocardial ischemia.

Sjögren's syndrome is often associated with neuropathic autonomic manifestations, the most prevalent being pupillomotor abnormalities, sweating reduction, and orthostatic hypotension. These may appear in the setting of a pure autonomic neuropathy or as an additional feature of sensory ataxia and painful or trigeminal neuropathies. Interestingly, these manifestations may frequently precede the diagnosis of sicca syndrome [36].

Peripheral neuropathies with autonomic manifestations may also arise in the absence of obvious underlying disorders. The frequent detection of autoantibodies, as well as the clinical overlap with acute inflammatory demyelinating polyneuropathy or paraneoplastic syndromes, has pointed towards an immunological etiology of these conditions. Different entities have been described on the basis of clinical presentation, which may range from an exclusive autonomic dysfunction to mixed autonomic and sensory or sensory motor manifestations [30]. The best characterized entity is represented by autoimmune autonomic ganglionopathy (AAG), previously known as acute pandysautonomia [66]. AAG is associated in up to 50% of the patients with an antiganglionic acetylcholine receptor antibody, which probably plays a direct pathogenetic role as autoantibody levels are closely related to disease severity and remission. The disease usually features an almost exclusive autonomic presentation with orthostatic intolerance and gastrointestinal dysmotility as a prominent manifestations [30].

Take Home Messages

- Autonomic disorders have a multifaceted presentation which may overlap with common non-autonomic medical conditions. A careful history taking and examination is the first milestone to guide clinical work-up.
- The early onset of a progressive, severe autonomic failure in the setting of a parkinsonian or a cerebellar syndrome is highly suggestive for multiple system atrophy
- Autonomic disturbances feature in a variety of peripheral neuropathies secondary to acquired or congenital metabolic disorders (e.g. diabetes, Fabry' disease), autoimmune diseases (Sjogren's syndrome, systemic lupus erythematosus), toxic or infectious causes.
- An acute or subacute onset of autonomic symptoms should prompt exclusion of a paraneoplastic cause. An autoantibodies panel and ad hoc imaging studies should be performed.

References

1. Adams-Carr KL, Bestwick JP et al (2015) Constipation preceding Parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 87(7):710–716
2. Antoine JC, Camdessanche JP (2007) Peripheral nervous system involvement in patients with cancer. Lancet Neurol 6(1):75–86
3. Brignole M (2007) Diagnosis and treatment of syncope. Heart 93(1):130–136
4. Callaghan BC, Cheng HT et al (2012) Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 11(6):521–534
5. Cersosimo MG, Raina GB et al (2011) Dry mouth: an overlooked autonomic symptom of Parkinson's disease. J Parkinsons Dis 1(2):169–173
6. Cheshire WP, Freeman R (2003) Disorders of sweating. Semin Neurol 23(4):399–406
7. Colosimo C, Morgante L et al (2010) Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. J Neurol 257(1):5–14
8. de Boer RD, Marinus J et al (2011) Distribution of signs and symptoms of complex regional pain syndrome type I in patients meeting the diagnostic criteria of the International Association for the Study of Pain. Eur J Pain 15(8):830 e831–830 e838
9. Fanciulli A, Gobel G et al (2016) Supine hypertension in Parkinson's disease and multiple system atrophy. Clin Auton Res 26(2):97–105
10. Fanciulli A, Strano S et al (2013) The potential prognostic role of cardiovascular autonomic failure in alpha-synucleinopathies. Eur J Neurol 20(2):231–235
11. Fanciulli A, Strano S et al (2014) Detecting nocturnal hypertension in Parkinson's disease and multiple system atrophy: proposal of a decision-support algorithm. J Neurol 261(7):1291–1299
12. Fanciulli A, Wenning GK (2015) Multiple-system atrophy. N Engl J Med 372(14):1375–1376
13. Fasano A, Visanji NP et al (2015) Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 14(6):625–639
14. Fowler CJ (2007) Update on the neurology of Parkinson's disease. NeurourolUrodyn 26(1): 103–109
15. Freeman R (2005) Autonomic peripheral neuropathy. Lancet 365(9466):1259–1270
16. Freeman R (2008) Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med 358(6):615–624
17. Freeman R, Wieling W et al (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 21(2):69–72
18. Gacci M, Eardley I et al (2011) Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 60(4):809–825
19. Garland EM, Celedonio JE et al (2015) Postural tachycardia syndrome: beyond orthostatic intolerance. Curr Neurol Neurosci Rep 15(9):60
20. Garland EM, Hooper WB et al (2013) Pure autonomic failure. Handb Clin Neurol 117:243–257
21. Gibbons CH, Freeman R (2015a) Clinical implications of delayed orthostatic hypotension: a 10-year follow-up study. Neurology 85(16):1362–1367
22. Gibbons CH, Freeman R (2015b) Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain 138(Pt 1):43–52
23. Gilman S, Wenning GK et al (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71(9):670–676
24. Goldstein DS, Pechnik S et al (2003) Association between supine hypertension and orthostatic hypotension in autonomic failure. Hypertension 42(2):136–142
25. Jecmenica-Lukic M, Poewe W et al (2012) Premotor signs and symptoms of multiple system atrophy. Lancet Neurol 11(4):361–368
26. Jost WH, Muller-Lobeck H et al (1998) Involuntary contractions of the striated anal sphincters as a cause of constipation: report of a case. Dis Colon Rectum 41(2):258–260

27. Kaufmann H, Malamut R et al (2012) The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res 22(2):79–90
28. Kenny RA, Shaw FE et al (2004) Carotid sinus syndrome is common in dementia with Lewy bodies and correlates with deep white matter lesions. J Neurol Neurosurg Psychiatry 75(7):966–971
29. Kimber J, Mathias CJ et al (2000) Physiological, pharmacological and neurohormonal assessment of autonomic function in progressive supranuclear palsy. Brain 123(Pt 7):1422–1430
30. Koike H, Watanabe H et al (2013) The spectrum of immune-mediated autonomic neuropathies: insights from the clinicopathological features. J Neurol Neurosurg Psychiatry 84(1):98–106
31. Kollensperger M, Geser F et al (2008) Red flags for multiple system atrophy. Mov Disord 23(8):1093–1099
32. Low PB, Benarroch EE (2008) Clinical autonomic disorders. Wolters Kluver-Lippincott-Williams & Wilkins, Philadelphia
33. Mathias CJ, Low DA et al (2012) Postural tachycardia syndrome--current experience and concepts. Nat Rev Neurol 8(1):22–34
34. McKeith IG, Dickson DW et al (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65(12):1863–1872
35. Meissner WG, Vital A et al (2010) Dyspnea as first sign of autonomic failure in postmortem confirmed multiple system atrophy. Mov Disord 25(12):1997–1998
36. Mori K, Iijima M et al (2005) The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain 128(Pt 11):2518–2534
37. Mostile G, Jankovic J (2009) Treatment of dysautonomia associated with Parkinson's disease. Parkinsonism Relat Disord 15(Suppl 3):S224–S232
38. Novakovic D, MacKay S (2015) Adult obstructive sleep apnoea and the larynx. Curr Opin Otolaryngol Head Neck Surg 23(6):464–469
39. Oertel WH, Wachter T et al (2003) Reduced genital sensitivity in female patients with multiple system atrophy of parkinsonian type. Mov Disord 18(4):430–432
40. Pareyson D, P Saveri, et al (2014) Charcot-Marie-Tooth disease and related hereditary neuropathies: from gene function to associated phenotypes. Curr Mol Med. PMID: 25323870
41. Pavy-Le Traon A, Amarenco G et al (2011) The Movement Disorders task force review of dysautonomia rating scales in Parkinson's disease with regard to symptoms of orthostatic hypotension. Mov Disord 26(11):1985–1992
42. Pavy-Le Traon A, Piedvache A et al (2015) New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study. J Neurol Neurosurg Psychiatry 87(5):554–561
43. Pfeifer MA, Weinberg CR et al (1984) Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 7(5):447–453
44. Ranieri M, Bedini G et al (2016) Fabry disease: recognition, diagnosis, and treatment of neurological features. Curr Treat Options Neurol 18(7):33
45. Robertson D, Haile V et al (1991) Dopamine beta-hydroxylase deficiency. A genetic disorder of cardiovascular regulation. Hypertension 18(1):1–8
46. Sakakibara R, Panicker J et al (2015) A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. NeurourolUrodyn 35(5):551–563
47. Schmidt C, Herting B et al (2008) Autonomic dysfunction in patients with progressive supranuclear palsy. Mov Disord 23(14):2083–2089
48. Shimohata T, Shinoda H et al (2007) Daytime hypoxemia, sleep-disordered breathing, and laryngopharyngeal findings in multiple system atrophy. Arch Neurol 64(6):856–861
49. Shimoyama M, Ohtahara A et al (2002) Isolated autonomic cardiovascular neuropathy in a patient with primary Sjogren syndrome: a case of successful treatment with glucocorticoid. Am J Med Sci 324(3):170–172
50. Sletten DM, Suarez GA et al (2012) COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc 87(12):1196–1201

51. Struhal W, Javor A et al (2014) The phoenix from the ashes: cardiovascular autonomic dysfunction in behavioral variant of frontotemporal dementia. J Alzheimers Dis 42(3): 1041–1046
52. Szewczyk-Krolikowski K, Tomlinson P et al (2014) The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. Parkinsonism Relat Disord 20(1):99–105
53. Szmulewicz DJ, McLean CA et al (2014) Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. Neurology 82(16):1410–1415
54. Task Force for the Diagnosis and Management of Syncope et al (2009) Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 30(21):2631–2671
55. Thaisetthawatkul P, Boeve BF et al (2004) Autonomic dysfunction in dementia with Lewy bodies. Neurology 62(10):1804–1809
56. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord. 2003;18(1):19–31.
57. van Dijk JG, Thijs RD et al (2014) The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. Brain 137(Pt 2):576–585
58. Vinik AI, Maser RE et al (2003) Diabetic autonomic neuropathy. Diabetes Care 26(5): 1553–1579
59. Vinik AI, Ziegler D (2007) Diabetic cardiovascular autonomic neuropathy. Circulation 115(3):387–397
60. Vodusek DB (2014) Lower urinary tract and sexual dysfunction in neurological patients. Eur Neurol 72(1–2):109–115
61. Wenning GK, Tison F et al (2004) Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 19(12):1391–1402
62. Wickremaratchi MM, Perera D, O'Loghlen C, Sastry D, Morgan E, Jones A, Edwards P, Robertson NP, Butler C, Morris HR, Ben-Shlomo Y. Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis. J Neurol Neurosurg Psychiatry. 2009;80(7):805–7.
63. Wieling W, Thijs RD et al (2009) Symptoms and signs of syncope: a review of the link between physiology and clinical clues. Brain 132(Pt 10):2630–2642
64. Wu TY, Taylor JM et al (2014) Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia 'CANVAS' syndrome. Brain 137(Pt 10):2649–2656
65. Yamashita F, Hirayama M et al (2010) Pupillary autonomic dysfunction in multiple system atrophy and Parkinson's disease: an assessment by eye-drop tests. Clin Auton Res 20(3): 191–197
66. Young RR, Asbury AK et al (1975) Pure pan-dysautonomia with recovery. Description and discussion of diagnostic criteria. Brain 98(4):613–636
67. Yuan D, Spaeth EB et al (2014) Disproportionate pupillary involvement in diabetic autonomic neuropathy. Clin Auton Res 24(6):305–309
68. Yuki N, Hartung HP (2012) Guillain-Barre syndrome. N Engl J Med 366(24):2294–2304
69. Ziegler D, Behler M et al (2015) Near-normoglycaemia and development of neuropathy: a 24-year prospective study from diagnosis of type 1 diabetes. BMJ Open 5(6):e006559

The Diagnosis and Management of Cardiovascular Autonomic Dysfunction and Disease

3

Ellen Merete Hagen and Judith Navarro-Otano

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E.M. Hagen, MD, PhD (✉)
Autonomic Unit, National Hospital for Neurology and Neurosurgery, UCLH, Queen Square, London, UK
e-mail: EllenMerete.Hagen@uclh.nhs.uk

J. Navarro-Otano, MD, PhD
Autonomic Unit, National Hospital for Neurology and Neurosurgery, UCLH, Queen Square, London, UK

Neurology Department, Hospital Clinic, Barcelona, Spain

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3.1 Diagnostic Approaches to Cardiovascular Autonomic Diseases

3.1.1 History, Neurological and General Evaluation, and ECG Assessment

Cardiovascular autonomic dysfunction and disease may affect only one organ or system but may be an important feature of underlying neurological disorder [2]. Cardiovascular autonomic dysfunction is a common part of many neurological disorders and is often the most disabling part of the disorder.

This chapter outlines the diagnostic approach to the most common cardiovascular autonomic dysfunctions, hypotension, autonomically mediated (or reflex) syncope, postural tachycardia syndrome (PoTS), and autonomic failure, and how to manage these by the use of both non-pharmacological measurements and pharmacological measurements.

The clinical picture of autonomic failure is usually dominated by disabling orthostatic hypotension (OH). Severely affected patients are able to stand only for a few seconds because of dramatic blood pressure (BP) falls produced by impaired cardiovascular adaption to upright posture [3].

Patients with autonomic failure share a similar clinical presentation; they are unable to tolerate upright posture because of severe orthostatic hypotension. It is however important to distinguish the different syndromes associated with autonomic failure because they differ in their disease pathophysiology, response to pharmacological treatment, and prognosis.

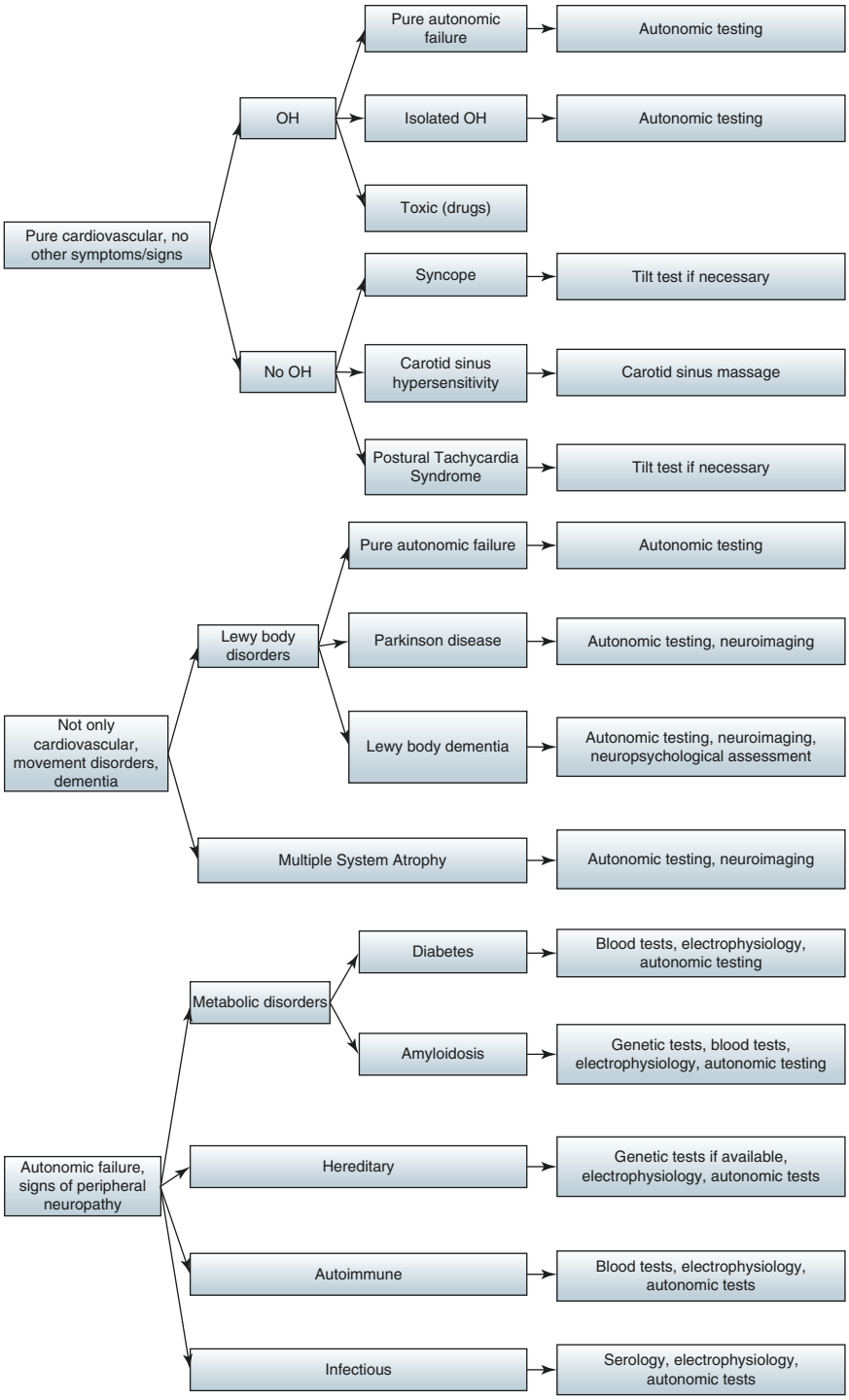
Virtually any disease that affects peripheral nerve function can produce autonomic failure.

Disorders associated with autonomic failure can be classified according to the type and severity of autonomic manifestations, associated neurological symptoms, and temporal profile [1].

Orthostatic hypotension (OH) is a prominent feature of autonomic failure, and it is often the symptom that leads the patient to seek medical advice. OH, also called postural hypotension, is a temporary lowering of blood pressure (hypotension), usually due to standing up suddenly (orthostatic). The change in position causes a temporary reduction in blood flow and oxygen to the brain. Upon standing gravity promotes the pooling of blood in the lower extremities, which decreases venous return of blood circulating back to the heart. Normally, cardiac and carotid sinus baroreceptors sense the decrease in blood volume and initiate increased heart rate and peripheral vasoconstriction.

In individuals with OH, there is an impaired efferent sympathetic signal to the arterioles and a failure to release norepinephrine appropriately upon standing. The consequent vasoconstrictor insufficiency results in blood pooling in the lower extremities, with subsequent decreased venous return to the heart and brain.

OH can be confirmed by measuring blood pressures and heart rate in supine and upright positions. BP and heart rate should be measured after symptoms develop or



Adapted from Benarroch [1]

after 3 min of standing. If the patient is unable to stand, testing for orthostatic hypotension may be done after the patient has risen to a sitting position with the feet dangling over the edge of the bed [4].

3.1.2 What Clinical Signs Hint to a Cardiovascular Autonomic Disease?

- Severe orthostatic hypotension
- Postprandial hypotension
- Supine hypertension
- High blood pressure variability
- Blunted heart rate variability
- Often a "non-dipping" or "reverse dipping" pattern on 24-h ambulatory blood pressure monitoring
- Medications influencing the cardiovascular autonomic nervous system/polypharmacy

3.2 What Can I Differentiate Already at Bedside and How Do I Manage the Patient?

3.2.1 Hypotension

Hypotension is the most common symptom of all cardiovascular autonomic dysfunctions. It can be the only symptom, it can occur together with syncope and postural tachycardia syndrome (PoTS), or it may be the initial sign of autonomic failure in both primary and secondary disorders of the autonomic nervous system (ANS): pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease (PD), dementia with Lewy bodies, autoimmune autonomic ganglionopathy, amyloidosis, and diabetic autonomic neuropathy [5]. The prevalence of OH increases with age [6].

Common secondary causes are spinal cord injury (SCI), stroke, multiple sclerosis (MS), Guillain–Barré syndrome, motor neuron disease, adrenal insufficiency, and vitamin deficiencies (e.g. B1, B12).

Non-neurogenic causes are volume depletion, pump failure, drugs, mitral valve prolapse, electrolyte disturbance, prolonged bed rest, pregnancy, and alcohol [2].

3.2.1.1 Orthostatic Hypotension

Definition

Orthostatic hypotension (classic) (OH) is defined as a sustained drop in blood pressure (BP) of greater than 20 mmHg systolic or 10 mmHg diastolic 3 min after rising

to a standing position from a supine position [4]. OH is an inability to maintain sufficient BP and adequate cerebral perfusion against gravity.

In neurogenic OH the heart rate response to changes in blood pressure is minimal, although there may be a mild compensatory increase, i.e. below 30 beats per minute.

Immediately after standing, there is gravitationally mediated redistribution of the blood volume and a pooling of 300–800 ml of blood in the lower extremities and splanchnic venous system [7]. This results in decreased stroke volume, as well as decreased systolic pressure and increased diastolic pressure.

"Initial OH" is characterised by a BP decrease immediately on standing of >40 mmHg systolic and/or >20 mmHg diastolic. BP then spontaneously and rapidly returns to normal, so the period of hypotension and symptoms is short (<30 s) [8, 9]. To confirm the presence of initial OH, BP must be recorded continuously (beat to beat) ideally in an autonomic laboratory. Bedside tests are not available.

"Delayed (progressive) OH" is not uncommon in elderly persons [10] and in patients with spinal cord injuries (SCI) [11]. Recent studies from Gibbons and Freeman [12] and Pavy-Le Traon [13] found a 10-year conversion rate to OH and higher prevalence of delayed OH in possible vs. probable MSA, respectively.

It is characterised by a slow progressive decrease in systolic BP on assuming erect posture. The absence of a bradycardiac reflex (vagal) differentiates delayed OH from reflex syncope. Delayed OH may be followed by reflex bradycardia [9].

In recently injured tetraplegics (2–13 days post injury), the basal supine level of blood pressure usually is lower than normal (mean arterial pressure, 57 mmHg in tetraplegics and 82 mmHg in normal subjects) [14]. Also in recently injured tetraplegics, the basal heart rate is usually <100 beats/min [15]. Frankel et al. found an inverse correlation between level of lesions and both systolic and diastolic blood pressure [16].

For physiology see Sect. 1.2.1, for history taking see Sect. 2.2.1.1

Epidemiology

In an unselected population >65 years, the prevalence of OH was reported to be 5–30% [17].

The prevalence of symptomatic OH increased from 14.8% in persons aged 65–69 years to 26% in persons >85 years, signifying the association between symptomatic OH and ageing [18]. In other populations, such as in Parkinson's disease, the prevalence of OH may be as high as 60% [19]. The presence of OH increases risk for falls and all-cause mortality in middle-aged and elderly persons [20]. OH is an independent risk factor for cardiovascular morbidity and mortality from stroke, coronary heart disease, and chronic kidney disease [20].

Although symptoms of OH may include dizziness and syncope, asymptomatic OH is far more common and represents an independent risk factor for mortality and cardiovascular disease. In a prospective study of more than 33,000 individuals, asymptomatic OH was present in over 6% and was associated with

age, female sex, hypertension, antihypertension treatment, increased heart rate, diabetes, low body mass index, and recurrent smoking [21]. Those with OH had significantly greater risk for all-cause mortality, especially those younger than 42 years, and higher risk for coronary events. OH has a prognostic role on cognitive and cardio- and cerebrovascular outcome in α-synucleinopathies.

Non-neurogenic Causes of OH

Drugs are the main non-neurogenic cause of orthostatic hypotension. Reducing or changing medications may lead to significant improvement. The α-blockers attenuate the α-adrenergic response, which increases vascular resistance and therefore should be avoided. The prevalence of orthostatic hypotension with the use of calcium antagonists ranges from 1% to 7%. The rate is low with thiazide diuretics and β-blockers, and some β-blockers with intrinsic sympathomimetic activity may even improve orthostatic hypotension. The co-administration of loop diuretics with other antihypertensives increases orthostatic hypotension [20].

Drugs that may cause or aggravate orthostatic hypotension and syncope [22]:

- α-Adrenoceptor agonists (α-blockers)
- Antipsychotics
- β-blockers
- Nitrates
- Hypnotics
- ACE inhibitors
- Anaesthetics
- Angiotensin II antagonists
- Barbiturates
- Calcium antagonists
- Clonidine
- Diuretics
- Levodopa and dopamine agonists
- Methyldopa
- Nitrates
- Phenothiazines
- Sildenafil
- Tricyclic and MAOI antidepressants

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MAOI, monoamine oxidase inhibitor

Other non-neurogenic causes are low intravascular volume (blood or plasma loss, fluid or electrolyte loss), impaired cardiac function due to structural heart disease, and vasodilatation due to drugs, alcohol, heat, and bed rest [2, 23].

OH and tachycardia may occur after prolonged bed rest or following exposure to microgravity, such as in spaceflights [24].

Examination

The history is of particular importance and has a high diagnostic value (including pre-existing conditions, a detailed description of the order of symptoms, and exhaustive drug history including over-the-counter drugs) [5].

The European Federation of Neurological Societies (EFNS) guidelines on the diagnosis and management of OH [23] recommend the following actions:

- Structured history taking see Sect. 2.2.1.1
- Detailed physical examination
- 12-lead ECG recording
- Laboratory testing [25]:
  - Blood tests (HbA1C), oral glucose tolerance test, urea and electrolytes, thyroid-stimulating hormone, HIV serology, hepatitis C serology/viral load, ACE level, ANA, anti-Ro/La antibodies, rheumatoid factor/anti-cyclic citrullinated peptide antibodies, anti-tissue transglutaminase antibody, serum electrophoresis, vitamin B12 levels, leucocyte α-galactosidase A activity (Fabry's disease), lipid profile, erythrocyte sedimentation rate, and SAP (serum amyloid P component)
- Eventually additional tests are needed:
  - Genetic testing: SCN9A/SCN10A mutations and transthyretin mutations (familial amyloid)
  - Imaging: if malignancy or sarcoidosis suspected, chest X-ray/CT with contrast and SAP (Serum Amyloid P component) scan (amyloid)
  - Tissue biopsy: abdominal fat biopsy (amyloid), small bowel biopsy (coeliac disease), biopsy of suspicious lesion to confirm malignancy, lip biopsy (Sjögren's syndrome), and nerve biopsy (generally not performed unless there is large fibre involvement)
- BP measurements while supine and upright
- Cardiologic referral, if heart disease or abnormal ECG is present or suspected
- Active standing or head-up tilt (HUT), ideally with continuous assessment of BP and HR for 3 min
- Further ANS screening tests, with other appropriate investigations, depending on the possible aetiology of the underlying disorder

Non-neurogenic causes of OH must be considered, as they can exacerbate neurogenic OH [5].

Treatment of OH

General Management [5, 26]

Longitudinal studies have suggested that OH can increase the risk for stroke, myocardial ischaemia, and mortality. The therapeutic goal is to attenuate or eliminate symptoms rather than restore normotension.

Non-pharmacological Treatment

Non-pharmacological measurements are the basis for all interventions. Commonly before starting on any medication, the patient should have boosted the blood pressure by non-pharmacologic measurements first for a couple of months, i.e. venous compression, use of physical counter manoeuvres, and intermittent water bolus treatment. Treatment can be difficult, and the development of supine hypertension should be minimised, especially in patients with diabetes, heart failure, or cardiac ischaemia [20].

Standing upright results in translocation of between 500 and 700 mL of blood from central compartments to the lower limbs; this causes marked pressure differentials, with a substantial rise in pressure below and a fall in pressure above heart level [27]. It is essential to use adaptive mechanisms to ensure the maintenance of arterial blood pressure and in providing an adequate perfusion pressure to organs, to avoid malfunction especially while standing upright.

- Avoidance of factors that may induce OH, like elevated environmental temperatures (hot bath, hot shower, and sauna) which may cause venous pooling.
- Avoid prolonged recumbence during daytime.
- Avoid sudden head-up postural change (especially on waking when BP may be lowered by nocturnal polyuria) [28]. In the morning, move to head-up position slowly, sit on the edge of the bed for some minutes after recumbence, and activate calf muscles while supine.
- Two glasses of water on the bed table, slowly getting out of bed [29].
- Elevation of the bed head (20–30 cm) to avoid supine hypertension.
- High salt diet (6–10 g/day).
- High fluid intake (six to eight cups of water each day) [29].
- A small amount of coffee or tea is beneficial, coffee (one or two cups) after meals.
- Avoid alcohol.
- Avoid large meals (especially with refined carbohydrate).
- Maintain postural stimuli.
- Move slowly when sitting up or standing after lying down.
- Avoid standing for long periods of time.
- Physical counter manoeuvres (e.g. leg crossing on standing, gentle marching on the spot instead of standing still) (Fig. 3.1).
- Squatting to reduce blood pooling will effectively reduce OH temporarily [30, 31].
- Elastic stockings and abdominal compression bands reduce venous pooling [32].
- Avoid straining during micturition and defaecation. For males: moving to a sitting position for micturition. The use of prokinetic drugs to avoid constipation.
- Resting in morning and postprandial.
- Staged standing.
- Physical activity: carefully controlled and individualised exercise training (swimming, aerobics, cycling, and walking if possible) often improves OH.
- Correction of anaemia.

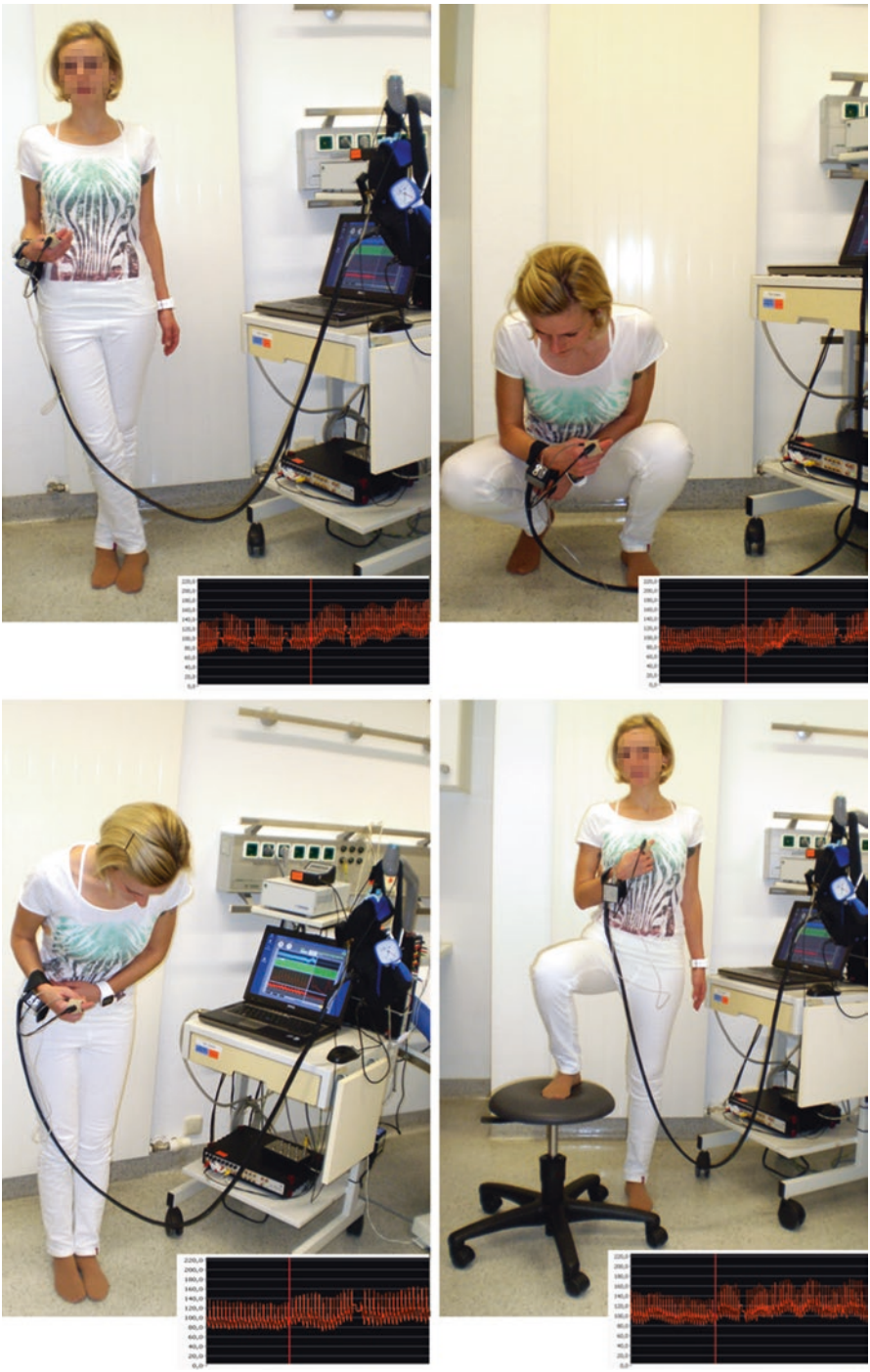
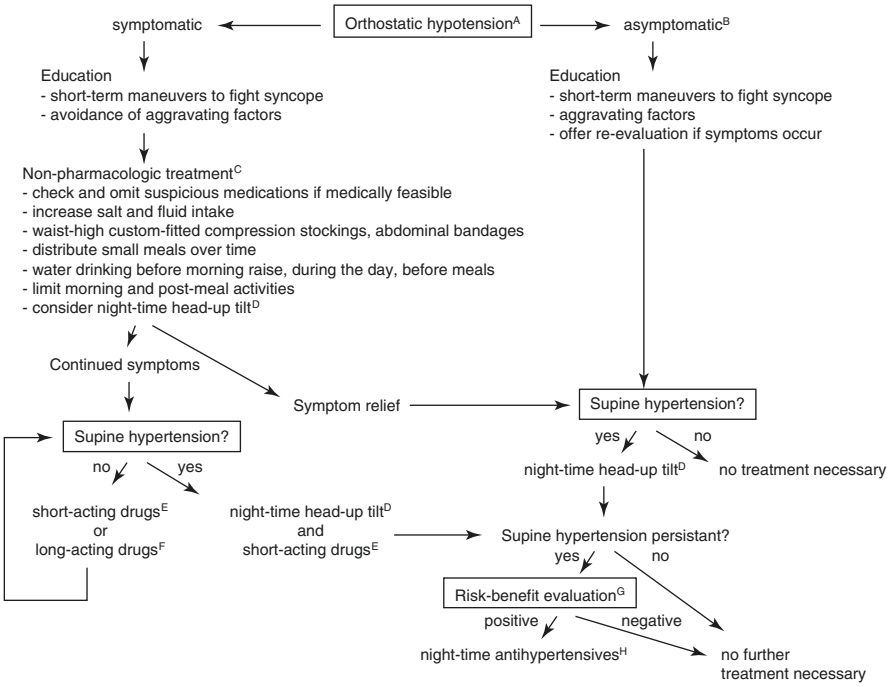


Fig. 3.1 Counter manoeuvre showing recommended poses: the trace shows beat to beat blood pressure recordings and consecutive changes after initiation of the counter manoeuvre: (**a**) leg crossing, (**b**) squatting, (**c**) bending, (**d**) foot on the chair

- Education of patients and carers on the mechanisms of OH.
- Black liquorice (3 g/day) (should not be used for a longer period due to potential hormonal side effects) [33].

Pharmacologic Treatment

Non-pharmacological treatment should always be optimised before starting on drugs. Strategies in pharmacological treatment are volume expansion, vasoconstriction, or combination of the two [20].



Printed with permission Schroeder et al. [34]

Volume expansion

- Fludrocortisone (0.1–0.3 mg/day) [19, 20, 35, 36]
- Desmopressin nasal spray (5–40 μg), orally (100–800 μg) or intramuscularly (2–4 μg) [37]

Vasoconstriction

- Midodrine (2.5–10 mg tds) [20, 23, 35]
- Pyridostigmine (60 mg tds) [35, 38]

- Ephedrine (25–50 mg tds) [23]
- Pseudoephedrine (30 mg qid) [23]
- Octreotide (12.5–25 μg, subcutaneous) – for postprandial hypotension – contra-indicated in diabetic patients [19, 39, 40]
- Droxidopa (L-DOPS) (100–600 mg tds) – presently only licenced in the USA and Japan [41–43]

Combination therapy

- Fludrocortisone (0.1–0.3 mg/day) and Midodrine (5–10 mg tds)
- Midodrine (5–10 mg) or Pseudoephedrine (30 mg) and water bolus

Other agents previously tried are:

- Yohimbine [19]
- Dihydroergotamine [44]
- Domperidone [19]
- Korodin [45]
- Atomoxetine [3]

3.2.1.2 Postprandial Hypotension (PPH)

Definition

Postprandial hypotension (PPH) was first described by Seyer-Hansen in a patient with severe Parkinson's disease in 1977 [46]. PPH is by definition a decrease in systolic blood pressure of ≥20 mm Hg or a decrease below 90 mm Hg from a pressure of ≥100 mm Hg within 2 h after a meal [39]. PPH can be detected by either a 24-h blood pressure profile or testing in the autonomic laboratory.

Studies have shown a prevalence of PPH in institutionalised elderly persons ranging from 25% to 67% [20, 47]. Patients with PAF, Parkinson's disease, MSA, postprandial syncope, diabetes, and SCI are also prone to PPH [39].

Risk Factors for Postprandial Hypotension [47]

- Medications
  - Polypharmacy (>3 medications)
  - Diuretics
- Meals
  - Carbohydrate-rich meals
  - Breakfast
  - Hot meals
  - Alcohol
- Comorbid conditions
  - Diabetes mellitus
  - Autonomic dysfunction

- Parkinson's disease
- Hypertension
- End-stage renal disease on haemodialysis
- Fragile X mutation

Treatment of PPH

Non-pharmacological Management [48]
- Drink water before meals.
- Eat frequently, smaller meals.
- Assume a recumbent or sitting position after a meal.
- Avoid large meals.
- Avoid alcohol before and after meal.
- Dietary modification, reduce refined carbohydrates.
- Water with the meal.
- Wear abdominal binders.

Pharmacological Management [26, 49]
- Caffeine 250 mg (two cups) either 30 min before the meal or by the end of the meal.
- Midodrine 10 mg with meal.
- Octreotide 25–50 μg subcutaneous 30 min before meal.
- α-Glucosidase inhibitor
  - Acarbose 25–100 mg tds [40].
  - Voglibose 0.2–0.5 mg tds [50].
- Guar gum 9 g [40].

3.2.1.3 Exercise-Induced Hypotension (EIH) and Post-exercise Hypotension (PEH)

Definition

Exercise-induced hypotension was first reported in autonomic failure patients cycling in supine position in 1961 by Shepherd and colleagues in a group of patients who performed supine cycling exercise [51].

Exercise-induced hypotension (EIH) is defined as a ≥10 mmHg fall in systolic blood pressure during exercise due to fall in total peripheral resistance [52]. Impairment of sympathetic vasoconstriction in autonomic failure has been documented as systemic vascular resistance falls substantially in the patients during exercise [53]. EIH can be a significant symptom in patients with PAF, MSA, and SCI. The severity of EIH seems to be higher during dynamic relative to static exercise [52].

Post-exercise hypotension (PEH) is defined as a reduction in systolic and/or diastolic arterial blood pressure (i.e. reduction in mean arterial pressure) below control levels after a single bout of exercise for approximately 1–3 h [54]. PEH has been well documented in humans with both borderline hypertension and hypertension [55], with diabetes [56], in healthy endurance training athletes [57],

and in SCI [58]. Data suggest that PEH may also occur after resistance exercise [55]. Studies have suggested that a reflex similar to the Bezold–Jarisch reflex is the final pathway triggering the vasovagal reaction in exercise-induced neurally mediated syncope [53]. The Bezold–Jarisch reflex is a triad of responses (apnoea, bradycardia, and hypotension) and depends on intact vagal nerves and is mediated through cranial part of medullary centres controlling respiration, heart rate, and vasomotor tone [59].

Treatment of EIH and PEH

Non-pharmacological Measurements

- Adequate hydration prior to exercise.
- Avoiding food intake for several hours before exercise to prevent postprandial hypotension.
- Increased daily salt intake [60].
- Prevention of dehydration after exercise by oral water intake during exercise [61].
- Muscle tensing [60].
- Use of abdominal compression/binders and lower limb elastic stockings [60].
- Mild physical exercise/activity [60].
- Reducing risk factors by exercise training in the supine position (swimming, rowing) [22, 52].

Pharmacological Measurements

Unfortunately there are limitations to pharmacological treatment in exercise-induced hypotension [52]. Both octreotide and midodrine did not show any effect on exercise-induced hypotension in studies; however, the increase in blood pressure overall may be beneficial in reducing fatigue [62].

In a small study with four patients with SCI (C6–C8), treatment with 10 mg Midodrine was associated with elevated systolic blood pressure during peak exercise in three participants. Two participants showed a concurrent decrease in perceived exertion and increase in oxygen consumption, suggestive of some benefit from Midodrine on EIH in SCI [63].

3.2.1.4 Supine Hypertension

Supine hypertension is a common finding in autonomic failure and complicates the treatment of the OH [64]. Supine hypertension can worsen OH and predispose to end-organ damage [65], resulting from medication and/or being part of the disease, especially in PAF.

Supine hypertension, defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, is present in one half of patients with severe autonomic failure, despite normal seated and low upright blood pressures [64, 66].

Nocturnal hypertension is defined as night-time BP means ≥120/70 mm Hg (fixed cut-off limits) [67]. A 24-h ambulatory BP monitor is needed to screen for

nocturnal hypertension and missing dipping and may be very useful before and if needed after starting a new therapy [68].

Ways to Counteract Supine Hypertension [65]
- Avoid supine position during daytime.
- Patients can sit in a reclining chair with feet on the floor when rest is needed.
- Avoid pressor medications after 16.00 h.
- Elevate the bed head (20–30 cm).
- Have a snack just before going to bed (inducing postprandial hypotension).
- If Fludrocortisone is used, this may worsen the supine hypertension. Changing to a short-acting pressor agent (e.g. Midodrine, Droxidopa, etc.) may sometimes be of help.

Avoid over-the-counter medications that increase blood pressure such as nasal decongestants or eye drops containing sympathomimetics and non-steroidal anti-inflammatory agents (indomethacin and ibuprofen).

Pharmacological Interventions (Single Dose Given at Bedtime)
- Losartan (angiotensin I receptor blocker), 50 mg at bedtime [70].
- Transdermal nitroglycerin, 0.05–0.2 mg/h only during night [3].
- Hydralazine, 50 mg [3].
- Short-acting nifedipine, 30 mg [3].
- Clonidine 0.1 mg early in the evening – Clonidine has a long half-life which may exacerbate morning OH [3].
- Sildenafil, 25 mg [3].
- Minoxidil, 2.5 mg [3].

3.2.2 Syncope

Syncope is defined as transient loss of consciousness due to global cerebral hypoperfusion. It is characterised by rapid onset, brief duration of loss of consciousness with spontaneous, and full recovery [9].

Syncope is a common medical problem, with a frequency between 15% and 39% [70]. In the general population, the annual number episodes are 18.1–39.7 per 1000 patients, with similar incidence between genders. The first report of the incidence of syncope is 6.2 per 1000 person-years [9], with a significant increased incidence after 70 years of age [70]. Syncope is responsible for 3–5% of emergency department visits [70].

The prognosis depends on the diagnosis [71]. If the patient has a structural heart disease or primary cardiac disease, there is an increased incidence of sudden death and overall mortality. If the syncope is caused by orthostatic hypotension, it is associated with a twofold increase in mortality, while young patients with neurally mediated syncope have a very good prognosis [71].

3.2.2.1 Classification

Causes of Syncope [72, 73]
Neurally mediated (vasovagal/reflex) syncope

(a) Vasodepressive
(b) Cardioinhibitory
(c) Mixed

Situational syncope (vasovagal in nature)

- Cough and sneeze
- Micturition (post-micturition)
- Post-exercise
- Postprandial

Gastrointestinal stimulation (*swallow*, *defaecation*, *visceral pain*)
Other (*laughter*, *brass instrument playing*, *weightlifting*)

- *Post-ejaculation*

Carotid sinus syncope

Orthostatic/postural syncope

(a) Autonomic failure
    - Primary autonomic failure syndromes (i.e. pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure, dementia with Lewy bodies)
    - Secondary autonomic failure syndromes (i.e. diabetic neuropathy, amyloid neuropathy)
    - Post-exercise
    - Postprandial
(b) Volume depletion
    - Haemorrhage, diarrhoea, and Addison's disease

Cardiac arrhythmias as primary cause

- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- Atrioventricular conduction system disease
- Paroxysmal supraventricular and ventricular tachycardias
- Inherited syndromes (i.e. long QT syndrome, Brugada syndrome)
- Implanted device (pacemaker, implantable cardioverter defibrillator) malfunction
- Drug-induced arrhythmias

Structural cardiac or cardiopulmonary disease

- Obstructive cardiac valvular disease
- Acute myocardial infarction/ischaemia
- Obstructive cardiomyopathy
- Atrial myxoma
- Acute aortic dissection
- Pericardial disease/tamponade
- Pulmonary embolus/pulmonary hypertension

Cerebrovascular

- Vascular steal syndromes
- Epilepsy with bradyarrhythmias/asystole (ictal asystole)

Non-cardiovascular/nonsyncopal causes of transient loss of consciousness

- Epileptic
- Non-epileptic ("sleep attacks")
- Metabolic disorders (hypoglycaemia)
- Neuroendocrine disorders (pheochromocytoma, carcinoid)
- Drugs
- Psychogenic pseudo-syncope and psychogenic non-epileptic seizure
- Traumatic

3.2.2.2 Neurally Mediated Syncope (Vasovagal/Reflex)

Vasovagal syncope was first used by William Gowers in 1907, and Thomas Lewin described the mechanism in 1932 [70]. The neurally mediated syncope, known as neurocardiogenic or vasovagal syncope, is the most frequent, accounting for one third of the causes and reaching 66% of cases of syncope in emergency units [70].

Neurally mediated syncope is characterised by periodic syncopal episodes with normal autonomic function between episodes. Symptoms that trigger syncope include orthostatic stress, prolonged standing, hot temperature, emotional stress, pain, or sight of blood. During neurally mediated syncope, vasodilatation and bradycardia occur simultaneously. The bradycardia is due to increased parasympathetic (vagal) outflow to the sinus node of the heart. The decrease in blood pressure is due to vasodilatation most likely by brainstem shut down of vascular sympathetic outflow, but the mechanism is not clear.

These reflex bradycardia and hypotension are similar to the response evoked by the Bezold–Jarisch reflex. The characteristic pre-syncopal symptoms are weakness, light-headedness, feelings of warmth or cold, and eventual brief loss of consciousness. Potential cardiac causes of syncope must be considered before making the diagnosis. Spontaneous syncope is common, and in the absence of any underlying

cardiovascular, neurologic, or other disease, an isolated vasovagal syncope may represent a variation of normal. The persons are usually normotensive with normal blood pressure regulation.

The diagnosis may sometimes be difficult to make. Situational syncope must be excluded, as well as phobia syndromes or other organic causes. Tilt table testing has good specificity but uncertain sensitivity in diagnosis and is not always reproducible. Implantable loop recorders, which store 45 min of retrospective electrocardiographic data, may also be used and can be activated by patients after each syncopal event.

Treatment of neurocardiogenic syncope is aimed at avoiding possible triggers. Information and education of the patients with special emphasis on potential predisposing factors and the recognition of prodromal symptoms are important. Education about possible pre-syncopal symptoms can help avert a syncopal episode by assuming a seated or supine position when possible. Increased fluid and salt intake may also help in avoiding the development of syncope and should always be tried first. Other non-pharmacological measurements include lower limb exercise, leg crossing, use of stockings, avoidance of triggers like heat, standing still for a long period, etc. Exercise and tilt training have been suggested.

In patient with the cardioinhibitory form, a dual-chamber pacemaker may be of value; however, the pacemaker will not improve the vasodepressor component of the syncope [74].

Pharmacotherapy includes β-blockers, which inhibit the activation of mechanoreceptors; Fludrocortisone, which expands central fluid volume via retention of sodium; and vasoconstrictors and selective serotonin reuptake inhibitors (SSRI) which may have a role in regulating sympathetic nervous system activity.

3.2.2.3 Carotid Sinus Syncope

Carotid sinus syndrome is associated with episodes of brief loss of consciousness, drop attacks, and unexplained falls without prodromal symptoms, especially in older males who often have cardiovascular disease [75]. It often occurs after neck movements, such as looking up or going down the stairs.

Carotid sinus syndrome is defined by a symptomatic 3 s asystole and/or a 50 mmHg reduction in systolic blood pressure (SBP) in response to carotid sinus massage (CSM) [76]. The syncope is caused by carotid sinus hypersensitivity resulting from stimulation of carotid sinus baroreceptors located in the internal carotid artery above the bifurcation of the common carotid artery. The presence of asymptomatic asystole or drop in BP during the CSM is not a diagnosis of carotid sinus hypersensitivity. CSM should be performed in the supine position and, if negative, repeated with the patient in the upright position [77]. The sensitivity of the CSM is increased by 31–52%, if it's performed while the patient is tilted 60–70° upright [77].

Carotid sinus syndrome is present in 8.8% of patients with cardiac syncope of all types. It represents 10% of unexplained syncope by the initial evaluation and 5% after the final diagnosis [77], with a rightsided preponderance [77], with a

right-sided preponderance. A study found that >70% of all the patients had a positive CSM on the right [75].

Treatment

Most patients can be treated with education, lifestyle changes, expectancy, and routine follow-up. If there are recurrent symptoms, the patient may need treatment.

Therapy can be divided into medical, surgical (carotid denervation), and pacing.

Medical treatment includes anticholinergics which blunt the bradycardia, Fludrocortisone, Ergotamine, Ephedrine to increase the blood pressure, and β-blockers and serotonin reuptake inhibitors (SSRI) which decrease both peripheral elements of the carotid sinus reflex [78].

Surgical denervation of the carotid sinus was previously used as treatment for carotid sinus syncope since the 1950s but is now abandoned [78].

Cardiac pacing has emerged as the primary therapy for patients with cardioinhibitory syncope, but may have an effect in patients with carotid sinus syncope as well [78, 79].

3.2.2.4 Situational Syncope

Situational syncope is diagnosed if syncope occurs during or immediately after urination, defaecation, cough, or swallowing [73, 80]. The precipitating causes are not always clear. Many of the incidents are related to the loss of intrathoracic pressure leading to syncope or Valsalva-like manoeuvres. A typical profile of the cough syncope patient based on the literature is that of a middle-aged, large-framed, or overweight male with obstructive airways disease [81].

Treatment

Management includes reducing or preventing exposure to precipitating causes, although these may be unclear. In some, especially those with phobias, behavioural therapy is needed.

The defaecation syncope is due to raised intra-abdominal pressures and Valsalva-type responses, and the use of abdominal binders may counteract this response [82].

3.2.3 Postural Tachycardia Syndrome (PoTS)

Postural tachycardia syndrome (PoTS) is primarily characterised by the development of tachycardia and orthostatic symptoms, with postural changes in the absence of significant hypotension.

PoTS as a condition was recognised by Rosen and Cryer in 1982 [62, 83] and later in 1993 by Schondorf and Low [84]. The most important symptom is orthostatic intolerance due to intermittent cardiovascular autonomic dysfunction [85].

The symptoms include palpitations, dizziness, and, in some patients, syncope, usually upon standing, and may be exacerbated by modest exertion, food ingestion, and heat.

PoTS affects predominantly young females, 5:1 ratio over males, and most patients are between 20 and 40 years of age [85]. There is a strong link to joint hypermobility syndrome, also known as Ehlers–Danlos syndrome (EDS) type III or Joint Hypermobility Syndrome. Symptoms may be brought on by infection, trauma, surgery, or stress. Possible pathophysiological mechanisms include alterations in neural control, humoral factors, vascular properties, and intravascular volume, as well as physical deconditioning [85].

PoTS is not a unique entity but the common presentation of a number of different causes. In addition, PoTS may be more subclassified as presented here. However, for the purpose of this book to present autonomic diagnostics at bedside, this would lead too far.

3.2.3.1 Frequent Reported Symptoms of PoTS [85]

- Dizziness and light-headedness
- Palpitations
- Visual disturbances
- Clumsiness
- Loss of consciousness
- Nausea
- Headache
- Pain (chest or upper abdomen)
- Shortness of breath
- Fatigue and lethargy
- Difficulty thinking or concentrating
- Psychiatric symptoms such as anxiety, panic attacks, and solitude

The symptoms are often relieved by lying flat.
Factors which may induce or worsen PoTS symptoms [85]

- Time of day (may be worse in the morning, especially on initial rising after wakening)
- Speed of positional change
- Raised temperature (hot weather, hot bath)
- Dehydration
- Food ingestion
- Alcohol
- Physical exertion
- Menstrual period
- Deconditioning or prolonged recumbence
- Drugs that cause vasodilatation

For further remarks on history taking see Sects. 2.2.1.1 and 2.3.2

3.2.3.2 Diagnostic Criteria for PoTS

PoTS is defined by a symptomatic heart rate increment of >30 beats/min or more within 10 minutes of standing or head-up tilt (HUT) in the absence of orthostatic

hypotension; the standing heart rate is often 120 beats/min or higher [86]. For individuals aged 12–19 years, the required increment is ≥40 beats/min [86].

The excessive tachycardia during orthostatic stress seen in patient with PoTS is a physiologic response that helps maintain arterial pressure during venous pooling. Patients with PoTS also demonstrate excessive tachycardia during exercise, which does not appear to be secondary to abnormal baroreflex regulation of the heart rate. Orthostatic intolerance is potentiated after deconditioning (spaceflight or prolonged bed rest).

Treatment

A multifactorial treatment strategy that includes pharmacological agents as well as non-pharmacological measures and interventions is often required. The approach should be pragmatic and holistic and focus on self-management. The patient should be taught to recognise triggers and manage and prevent symptoms. Exercise training and improved physical conditioning is an important strategy for PoTS as well as other deconditioned patients.

Non-pharmacological measurements to prevent hypotension and counteract tachycardia are increased fluid and salt intake, lower limb exercise, counterpressure manoeuvres, and the use of stockings. Gentle and gradual increasing core strengthening exercises like Pilates and swimming may be useful, especially for those with a diagnosis of Ehlers–Danlos syndrome (EDS) type III.

Pharmacological treatment approaches for PoTS are similar to those used for orthostatic hypotension, including Fludrocortisone, Ephedrine, and Midodrine, and low-dose β-blockers or Ivabradine. Associated disorders, such as the joint hypermobility syndrome and pain, need to be addressed. With time many patients get less symptomatic.

3.3 How to Manage Cardiovascular Autonomic Dysfunction and Disease?

Management depends on the underlying cause. After a review of a patient's medications for drugs that may contribute to syncope, rehydration, correction of any metabolic abnormality, and blood transfusion are appropriate first steps. Many medications are implicated, and stopping these should be considered. Further management includes non-pharmacological and pharmacological treatments. Although other medications have been studied, Fludrocortisone and Midodrine have accrued the best evidence for efficacy.

3.3.1 Overview of Non-pharmacological Measures

3.3.1.1 Water and Salt

Water drinking elicits a large, acute, pressor response in patients with autonomic failure who experience severe orthostatic hypotension [87]. Drinking water and increasing salt intake increase plasma volume, which helps maintain blood pressure upon standing.

The increase in blood pressure is evident within 5 min after drinking water, reaches a maximum after approximately 20–30 min, and is sustained for more than 60 min [87]. The recommended daily intake of water is 1.5–2.0 L/day and of sodium chloride is 6–10 g either incorporated into meals or taken as supplement tablets [88].

3.3.1.2 Orthostatic Training

The prescription of progressively prolonged periods of enforced upright posture may reduce the recurrence of neurally mediated syncope [88, 89]. However the patients need to be highly motivated when participating [90].

3.3.1.3 Counterpressure Manoeuvres

Counterpressure manoeuvres are simple ways to induce a significant blood pressure increase to counteract orthostatic hypotension, neurally mediated syncope, and PoTS [90, 88].

Countermeasures which are able to induce significant blood pressure increase include:

- Clenching the teeth
- Squeezing the buttocks
- Isometric hand grip and arm tensing
- Leg crossing on standing
- Gentle marching on the spot instead of standing still
- Squatting

3.3.1.4 Raising the Head of the Bed

Raising the head of the bed 10–20° activates the renin–angiotensin–aldosterone system [88, 91] and decreases the nocturnal diuresis. Raising the head of the bed may also reduce the supine hypertension that is prevalent in patients suffering from cardiovascular autonomic dysfunction, either as a consequence of baroreceptor denervation or as a side effect of treatment [92].

3.3.1.5 Compression Stockings

The rationale for compression therapy is to reduce venous pooling in the lower extremities to promote venous return and cardiac output. The categories of compression stockings include knee-length, thigh-length, full-length, and abdominal compression. The current literature reports the use of waist-high stockings that afford abdominal compression is needed to affect cardiovascular dynamics at the onset of head-up tilt and may prevent OH [93].

Although compression stockings provide orthostatic relief, there may be difficulties with compliance. Full-length compression stockings are uncomfortable and may be a burden to put on and wear. If the patient is able to comply, compression stockings should be incorporated in the treatment regimen for orthostatic hypotension. Ideally, abdominal compression should also be included because there is often considerable pooling in the splanchnic circulation. Fanciulli et al. found an elastic abdominal binder significantly reduced blood pressure fall upon tilting in OH

associated with Parkinson's disease (PD) [94]. In our experience, patients prefer compression stockings that do not cover the feet.

3.3.2 Overview of Pharmacological Measurements

Pharmacological treatment should only be initiated when sufficient control can't be achieved by non-pharmacological measurements.

3.3.2.1 Fludrocortisone

Fludrocortisone acts as a systemic corticosteroid, increasing sensitivity to circulating catecholamines. Fludrocortisone is the first-line pharmacological treatment of OH, and it promotes a positive response in 40–75% of patients. It is also used as a first-line treatment in PoTS. It has central adrenergic effects and increases arteriolar sensitivity to catecholamine and angiotensin. The starting dose is 50 μg once daily, which is increased by 25–50 μg every 1–2 weeks to alleviate symptoms without incurring side effects.

The recommended dose is 100–300 μg/day, and it can take up to 5 days to see the full effects.

Higher doses that elevate circulating epinephrine can cause hypokalaemia and supine hypertension. Fludrocortisone is not recommended for patients with congestive heart failure or chronic renal failure.

Side effects include hypertension, oedema, hypokalaemia, depression, and headache. Electrolyte levels should be checked 1 week after starting Fludrocortisone and a week after a dose change.

3.3.2.2 Midodrine

Midodrine, a peripheral selective alpha-1-adrenergic agonist, significantly increases standing systolic blood pressure and improves symptoms in patients with neurogenic OH [95] and is used as second-line therapy in OH and in selected PoTS patients. Standing systolic blood pressure is elevated by approximately 15–30 mm Hg at 1 h after 10 mg dose, with some effect persisting for 2–3 h. Midodrine has no clinically significant effect on standing or supine pulse rates in patients with autonomic failure. It can be used as a fludrocortisone-sparing agent.

Midodrine acts as a pressor agent both on venous and arterial constrictions and is effective 1 h after ingestion. The recommended dose (typically given in the morning, noon, and afternoon to avoid supine hypertension in the evening) is up to 10 mg three times daily; each dose typically lasts for 4 h, consistent with blood levels of the active metabolite desglymidodrine. The initial usual dose is 2.5 mg three times daily, with a slow and progressive increment as needed.

The major adverse effect is supine hypertension. This adverse reaction can be minimised by taking it half an hour before standing up in the morning and avoiding becoming supine 4 h after each dose. Other reported adverse effects include pilo-erection, scalp pruritus, tingling, and urinary retention/urgency [96].

Midodrine is contraindicated during pregnancy and breastfeeding. Women in fertile age should be explained this contraindication prior to be started on it.

Increased central serotoninergic activity has been suggested to play a role in sudden inhibition of sympathetic activity, potentially precipitating neurally mediated syncope, especially in patients resistant to or intolerant of previous traditional therapies [97].

3.3.2.3 Ephedrine

Ephedrine has adrenergic effects on the circulation and increases the mean heart rate as well as the systolic and, slightly, diastolic arterial blood pressure [98]. Adverse effects are hypertension and thrombosis [96]. Recommended dosage is 15 mg three times daily.

3.3.2.4 Octreotide

Octreotide is a somatostatin analogue which attenuates the pancreatic and gastrointestinal hormone response to food ingestion [92].

It reduces the postprandial blood pressure fall and the orthostatic hypotension in patients with autonomic failure by local effect on splanchnic vasculature via inhibiting the release of vasoactive gastrointestinal peptides [92]. Adverse effects are diarrhoea, nausea, and abdominal cramps which limit the use [96]. Subcutaneous doses of octreotide range from 25 to 200 μg. It has been used in PoTS patients who are refractory to other treatments with some success.

Octreotide is contraindicated in pregnancy.

3.3.2.5 Erythropoietin

Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with OH. It also corrects the normochromic normocytic anaemia that frequently accompanies patients with autonomic failure [92]. Erythropoietin is not effective in the treatment of PoTS [99]. The mechanism of the pressor effect of this agent is unknown.

Adverse effects are supine hypertension and thrombosis [92, 96].

3.3.2.6 Droxidopa

Droxidopa (L-threo-dihydroxyphenylserine (DOPS)) is a synthetic prodrug that is converted into norepinephrine by the ubiquitous enzyme dopa decarboxylase. Droxidopa decreases postural drop in patients with orthostatic hypotension and reduces orthostatic symptoms [100].

Reported adverse effects are malignant neuroleptic syndrome, hypertension, and headache [96]. DOPS (200–400 mg daily) reduces OH with only minor side effects. It is an effective treatment in dopamine β-hydroxylase deficiency. Droxidopa is presently only licenced in the USA, Japan, and surrounding Asian areas.

3.3.2.7 Pyridostigmine

Pyridostigmine is a peripheral cholinesterase inhibitor that potentiates cholinergic transmission when the autonomic ganglia have already been engaged. It can cause

a mild increase in standing blood pressure without significantly increasing supine blood pressure. Administering pyridostigmine as needed may improve orthostatic hypotension without contributing to supine hypertension. Adverse effects are cholinergic, including diarrhoea, excessive sweating, and sialorrhoea [38].

The usual initial dose is 30 mg twice daily, which can be increased as tolerated up to 90 mg three times daily.

3.3.2.8 Domperidone

While dopamine agonists are widely used to manage Parkinson's symptoms, one major side effect is acute orthostatic hypotension after starting the treatment. Domperidone is a peripheral dopamine D2 receptor antagonist that is effective in treating acute orthostatic hypotension induced by dopamine agonists [101]. Adverse effects are worsening of Parkinson's motor symptoms and hyperprolactinaemia [96]. Domperidone is contraindicated in patients with underlying cardiac conditions because its use increases the risk of prolonged QT syndrome. Prolonged use is not recommended.

3.3.2.9 Yohimbine

Yohimbine is a centrally and peripherally active selective α2-adrenoreceptor antagonist that increases sympathetic nervous system efferent output [36]. Adverse effects are anxiety, tremor, palpitations, diarrhoea, and supine hypertension [96, 102]. Yohimbine increases norepinephrine spill-over from sympathetic nerve endings, leading to a normal increase in plasma norepinephrine levels in control subjects and in patients with MSA, but not in PD patients with OH and autonomic failure.

3.3.2.10 Atomoxetine

Atomoxetine is a norepinephrine transporter blocker thereby increasing synaptic norepinephrine concentration. It increases blood pressure in autonomic failure patients with residual sympathetic activity the first hour after its administration, although its use has not been tested at long term [103]. Adverse effects are nausea, dry mouth, appetite loss, insomnia, fatigue, headache, and cough. It is not licenced for use in OH either in the USA or Europe.

Co-administering Yohimbine with Atomoxetine can then enhance the pressor effect of Atomoxetine by potentiating the activity of the remaining sympathetic efferent fibres.

3.3.2.11 β-Blockers

β1-Selective (cardioselective) adrenoceptor blockers inhibits the activation of mechanoreceptor, leading to a reduction in both resting heart rate and exercise heart rate and decrease in blood pressure. β-Blockers have been used as therapy for neurally mediated syncope [90]. However β-blocker therapy might often worsen PoTS or reflex syncope considerably [90]. Adverse effects are cold hands and feet, tiredness, depression, impotence, vivid dreams, nightmares, and other sleep disturbances.

Take Home Messages

- OH is defined as fall in BP within 3 min of active standing or on head-up tilt. It is related to a shorter life expectancy.
- OH is often seen in primary neurodegenerative disorders (PAF, MSA, and PD) and other medical conditions (diabetes mellitus, dehydration) and due to vasoactive and also non-vasoactive drugs.
- Syncope is the most common autonomic cardiovascular disorder, mainly benign when there is no an underlying cardiac disease.
- Carotid sinus hypersensitivity should be suspected when the syncope is not preceded by typical warning symptoms, in elderly patients, and when the symptomatic episodes are related to neck movements.
- PoTS is common in young women, defined as a symptomatic excessive increase in heart rate (more than 30 beats per minute) during the first 10 min of standing or head-up tilt.
- Nocturnal hypertension can be seen due to the natural progression of the underlying disease or as a side effect of drug treatment.
- Individually tailored therapy is important in order to improve the patient's functional capacity and quality of life and preventing injury.
- Management includes education, advice, and training on various factors that influence blood pressure and special aspects that have to be avoided (foods, habits, positions, and drugs).
- Countermeasures including leg crossing, squatting, elastic abdominal binders, and stockings are useful.
- Both OH, syncope, and PoTS benefit from careful exercise.
- Increased water (1.5–2 l/day) and salt ingestion (6–10 g or 150 mmol/day).
- Always start with non-pharmacological measurements.
- First line drug of choice is Fludrocortisone. Sympathomimetics, such as Midodrine is second line.

References

1. Benarroch EE (2014) The clinical approach to autonomic failure in neurological disorders. Nat Rev Neurol 10(7):396–407
2. Mathias CJ (2003) Autonomic diseases: clinical features and laboratory evaluation. J Neurol Neurosurg Psychiatry 74(Suppl 3):iii31–iii41
3. Shibao C, Okamoto L, Biaggioni I (2012) Pharmacotherapy of autonomic failure. Pharmacol Ther 134(3):279–286
4. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology (1996) Neurology 46(5):1470
5. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M (2011) Orthostatic hypotension. In: Gilhus NE, Barnes MP, Brainin M, editors. European handbook of neurological management: volume 1. 2 ed: Blackwell Publishing Ltd.; p. 469–75
6. Gupta V, Lipsitz LA (2007) Orthostatic hypotension in the elderly: diagnosis and treatment. Am J Med. 120(10):841–847

7. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I et al (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 21(2):69–72
8. Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME (2007) Initial orthostatic hypotension: review of a forgotten condition. Clin Sci (Lond) 112(3):157–165
9. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB et al (2009) Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 30(21):2631–2671
10. Gibbons CH, Freeman R (2006) Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. Neurology 67(1):28–32
11. Claydon VE, Steeves JD, Krassioukov A (2006) Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology. Spinal Cord 44(6):341–351
12. Gibbons CH, Freeman R (2015) Clinical implications of delayed orthostatic hypotension: a 10-year follow-up study. Neurology 85(16):1362–1367
13. Pavy-Le Traon A, Piedvache A, Perez-Lloret S, Calandra-Buonaura G, Cochen-De Cock V, Colosimo C et al (2015) New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study. J Neurol Neurosurg Psychiatry 87(5):554–561
14. Mathias CJ, Christensen NJ, Frankel HL, Spalding JM (1979) Cardiovascular control in recently injured tetraplegics in spinal shock. Q J Med 48(190):273–287
15. Mathias CJ (2006) Orthostatic hypotension and paroxysmal hypertension in humans with high spinal cord injury. Prog Brain Res 152:231–243
16. Frankel HL, Michaelis LS, Golding DR, Beral V (1972) The blood pressure in paraplegia. I. Paraplegia 10(3):193–200
17. Low PA (2008) Prevalence of orthostatic hypotension. Clin Auton Res 18(Suppl 1):8–13
18. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS (1992) Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Hypertension 19(6 Pt 1):508–519
19. Senard JM, Brefel-Courbon C, Rascol O, Montastruc JL (2001) Orthostatic hypotension in patients with Parkinson's disease: pathophysiology and management. Drugs Aging 18(7):495–505
20. Arnold AC, Shibao C (2013) Current concepts in orthostatic hypotension management. Curr Hypertens Rep 15(4):304–312
21. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O (2010) Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). Eur Heart J 31(1):85–91
22. Maule S, Papotti G, Naso D, Magnino C, Testa E, Veglio F (2007) Orthostatic hypotension: evaluation and treatment. Cardiovasc Hematol Disord Drug Targets 7(1):63–70
23. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M (2006) EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 13(9): 930–936
24. Coupe M, Fortrat JO, Larina I, Gauquelin-Koch G, Gharib C, Custaud MA (2009) Cardiovascular deconditioning: From autonomic nervous system to microvascular dysfunctions. Respir Physiol Neurobi 169(Suppl 1):S10–SS2
25. Themistocleous AC, Ramirez JD, Serra J, Bennett DLH (2014) The clinical approach to small fibre neuropathy and painful channelopathy. Pract Neurol 14(6):368–379
26. Treatment Of Orthostatic Hypotension (1998) Continuum (Lifelong Learning in Neurology) 4(2):79–90
27. Mathias CJ (2002) To stand on one's own legs. Clin Med 2(3):237–245
28. Mathias CJ, Fosbraey P, da Costa DF, Thornley A, Bannister R (1986) The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. Br Med J (Clin Res Ed) 293(6543):353–354
29. Mathias CJ, Young TM (2004) Water drinking in the management of orthostatic intolerance due to orthostatic hypotension, vasovagal syncope and the postural tachycardia syndrome. Eur J Neurol 11(9):613–619

30. Groothuis JT, van Dijk N, Ter Woerds W, Wieling W, Hopman MT (2007) Leg crossing with muscle tensing, a physical counter-manoeuvre to prevent syncope, enhances leg blood flow. Clin Sci (Lond) 112(3):193–201
31. Wieling W, van Dijk N, Thijs RD, de Lange FJ, Krediet CT, Halliwill JR (2015) Physical countermeasures to increase orthostatic tolerance. J Intern Med 277(1):69–82
32. Podoleanu C, Maggi R, Brignole M, Croci F, Incze A, Solano A et al (2006) Lower limb and abdominal compression bandages prevent progressive orthostatic hypotension in elderly persons: a randomized single-blind controlled study. J Am Coll Cardiol 48(7):1425–1432
33. Basso A, Paola LD, Erle G, Boscaro M, Armanini D (1994) Licorice ameliorates postural hypotension caused by diabetic autonomic neuropathy. Diabetes Care 17(11):1356
34. Schroeder C, Jordan J, Kaufmann H (2013) Management of neurogenic orthostatic hypotension in patients with autonomic failure. Drugs 73(12):1267–1279
35. Ong AC, Myint PK, Shepstone L, Potter JF (2013) A systematic review of the pharmacological management of orthostatic hypotension. Int J Clin Pract 67(7):633–646
36. Freeman R (2008) Current pharmacologic treatment for orthostatic hypotension. Clin Auton Res. 18(Suppl 1):14–18
37. Freeman RR (2003) Treatment of orthostatic hypotension. Semin Neurol 23(4):435–442
38. Isaacson SH, Skettini J (2014) Neurogenic orthostatic hypotension in Parkinson's disease: evaluation, management, and emerging role of droxidopa. Vasc Health Risk Manag 10:169–176
39. Jansen RW, Lipsitz LA (1995) Postprandial hypotension: epidemiology, pathophysiology, and clinical management. Ann Intern Med 122(4):286–295
40. Ong AC, Myint PK, Potter JF (2014) Pharmacological treatment of postprandial reductions in blood pressure: a systematic review. J Am Geriatr Soc 62(4):649–661
41. Goldstein DS (2006) L-Dihydroxyphenylserine (L-DOPS): a norepinephrine prodrug. Cardiovasc Drug Rev 24(3–4):189–203
42. Kaufmann HH (2014) Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. Neurology 83(4):328–335
43. Mathias CJ (2008) L-dihydroxyphenylserine (Droxidopa) in the treatment of orthostatic hypotension: the European experience. Clin Auton Res. 18(Suppl 1):25–29
44. Hoeldtke RD, Cavanaugh ST, Hughes JD, Polansky M (1986) Treatment of orthostatic hypotension with dihydroergotamine and caffeine. Ann Intern Med 105(2):168–173
45. Kroll M, Ring C, Gaus W, Hempel B (2005) A randomized trial of Korodin Herz-Kreislauf-Tropfen as add-on treatment in older patients with orthostatic hypotension. Phytomedicine 12(6–7):395–402
46. Seyer-Hansen K (1977) Postprandial hypotension. Br Med J 2(6097):1262
47. Luciano GL, Brennan MJ, Rothberg MB (2010) Postprandial hypotension. Am J Med 123(3):281–286
48. Mathias CJ, Kimber JR (1998) Treatment of postural hypotension. J Neurol Neurosurg Psychiatry 65(3):285–289
49. Alagiakrishnan K (2007) Postural and Postprandial Hypotension: Approach to Management. Geriatr Aging 10(5):298–304
50. Maruta TT (2006) Voglibose inhibits postprandial hypotension in neurologic disorders and elderly people. Neurology 66(9):1432–1434
51. MARSHALL RJ, SCHIRGER A, Shepherd JT (1961) Blood pressure during supine exercise in idiopathic orthostatic hypotension. Circulation 24:76–81
52. Low DA, da Nóbrega ACL, Mathias CJ (2012) Exercise-induced hypotension in autonomic disorders. Auton Neurosci 171(1–2):66–78
53. Krediet CTP, Wilde AA, Wieling W, Halliwill JR (2004) Exercise related syncope, when it's not the heart. Clin Auton Res 14(Suppl 1):i25–i36
54. Kenney MJ, Seals DR (1993) Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension 22(5):653–664
55. MacDonald JR (2002) Potential causes, mechanisms, and implications of post exercise hypotension. J Hum Hypertens 16(4):225–236

56. Lima LCJ, Assis GV, Hiyane W, Almeida WS, Arsa G, Baldissera V et al (2008) Hypotensive effects of exercise performed around anaerobic threshold in type 2 diabetic patients. Diabetes Res Clin Pract 81(2):216–222
57. Liu S, Thomas SG, Sasson Z, Banks L, Busato M, Goodman JM (2013) Blood pressure reduction following prolonged exercise in young and middle-aged endurance athletes. Eur J Prev Cardiol 20(6):956–962
58. Rimaud D, Calmels P, Pichot V, Bethoux F, Roche F (2012) Effects of compression stockings on sympathetic activity and heart rate variability in individuals with spinal cord injury. J Spinal Cord Med 35(2):81–88
59. Aviado DM, Aviado DG (2001) The Bezold-Jarisch Reflex. Ann N Y Acad Sci 940(1):48–58
60. Figueroa JJ, Basford JR, Low PA (2010) Preventing and treating orthostatic hypotension: as easy as A, B, C. Cleve Clin J Med 77(5):298–306
61. Endo MY, Kajimoto C, Yamada M, Miura A, Hayashi N, Koga S et al (2012) Acute effect of oral water intake during exercise on post-exercise hypotension. Eur J Clin Nutr 66(11):1208–1213
62. Butler JE, Ribot-Ciscar E, Zijdewind I, Thomas CK (2004) Increased blood pressure can reduce fatigue of thenar muscles paralyzed after spinal cord injury. Muscle Nerve 29(4):575–584
63. Nieshoff EC, Birk TJ, Birk CA, Hinderer SR, Yavuzer G (2004) Double-blinded, placebo-controlled trial of midodrine for exercise performance enhancement in tetraplegia: a pilot study. J Spinal Cord Med 27(3):219–225
64. Jordan J, Biaggioni I (2002) Diagnosis and treatment of supine hypertension in autonomic failure patients with orthostatic hypotension. J Clin Hypertens (Greenwich) 4(2):139–145
65. Arnold AC, Biaggioni I (2012) Management approaches to hypertension in autonomic failure. Curr Opin Nephrol Hypertens 21(5):481–485
66. Fanciulli A, Göbel G, Ndayisaba JP, Granata R, Duerr S, Strano S et al (2016) Supine hypertension in Parkinson's disease and multiple system atrophy. Clin Auton Res 26(2):97–105
67. O'Brien EE (2005) Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. J Hypertens 23(4):697–701
68. Stuebner E, Vichayanrat E, Low DA, Mathias CJ, Isenmann S, Haensch CA (2013) Twenty-four hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's disease. Front Neurol 4:49
69. Arnold AC, Okamoto LE, Gamboa A, Shibao C, Raj SR, Robertson D et al (2013) Angiotensin II, independent of plasma renin activity, contributes to the hypertension of autonomic failure. Hypertension 61(3):701–706
70. da Silva RM (2014) Syncope: epidemiology, etiology, and prognosis. Front Physiol 5:471
71. Calkins HG, Zipes DP (2012) Hypotension and syncope. Braunwald's heart disease: a textbook of cardiovascular medicine. 10th ed. Saunders: Philadelphia, PA. p. 861–71
72. Bassetti CL (2014) Transient loss of consciousness and syncope. Handb Clin Neurol 119:169–191
73. Brignole M (2007) Diagnosis and treatment of syncope. Heart 93(1):130–136
74. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD et al (2012) Pacemaker therapy in patients with neurally mediated syncope and documented asystole: third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. Circulation 125(21):2566–2571
75. Tan MP, Newton JL, Reeve P, Murray A, Chadwick TJ, Parry SW (2009) Results of carotid sinus massage in a tertiary referral unit--is carotid sinus syndrome still relevant? Age Ageing 38(6):680–686
76. LOWN B, LEVINE SA (1961) The carotid sinus. Clinical value of its stimulation. Circulation 23:766–789
77. Sutton R (2014) Carotid sinus syndrome: progress in understanding and management. Glob Cardiol Sci Pract 2014(2):1–8
78. Healey J, Connolly S, Morillo C (2004) The management of patients with carotid sinus syndrome: is pacing the answer? Clin Auton Res 14(Suppl 1):i80–ii6

79. Romme JJ, Reitsma JB, Black CN, Colman N, Scholten RJ, Wieling W et al (2011) Drugs and pacemakers for vasovagal, carotid sinus and situational syncope. Cochrane Database Syst Rev 10:CD004194
80. van Lieshout JJ, ten Harkel AD, Wieling W (2000) Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure. Clin Auton Res 10(1):35–42
81. Dicpinigaitis PV, Lim L, Farmakidis C (2014) Cough syncope. Respir Med 108(2):244–251
82. Smit AA, Wieling W, Fujimura J, Denq JC, Opfer-Gehrking TL, Akarriou M et al (2004) Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. Clin Auton Res 14(3):167–175
83. Rosen SG, Cryer PE (1982) Postural tachycardia syndrome. Reversal of sympathetic hyper-responsiveness and clinical improvement during sodium loading. Am J Med 72(5):847–850
84. Schondorf R, Low PA (1993) Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? Neurology 43(1):132–137
85. Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R (2012) Postural tachycardia syndrome–current experience and concepts. Nat Rev Neurol 8(1):22–34
86. Freeman R, Kaufmann H (2007) Disorders of orthostatic tolerance-orthostatic hypotension, postural tachycardia syndrome, and syncope. Continuum (Lifelong Learning in Neurology) 13(6):50–88
87. Jordan J (2002) Acute effect of water on blood pressure. What do we know? Clin Auton Res. 12(4):250–255
88. Wieling W, Ganzeboom KS, Saul JP (2004) Reflex syncope in children and adolescents. Heart 90(9):1094–1100
89. Abe H, Kondo S, Kohshi K, Nakashima Y (2002) Usefulness of orthostatic self-training for the prevention of neurocardiogenic syncope. Pacing Clin Electrophysiol 25(10):1454–1458
90. Guzman JC, Armaganijan LV, Morillo CA (2013) Treatment of neurally mediated reflex syncope. Cardiol Clin 31(1):123–129
91. Smit AA, Halliwill JR, Low PA, Wieling W (1999) Pathophysiological basis of orthostatic hypotension in autonomic failure. J Physiol 519(Pt 1):1–10
92. Freeman R (2012) Treatment of orthostatic hypotension. Saunders 2015, Philadelphia
93. Tanaka K, Tokumiya S, Ishihara Y, Kohira Y, Katafuchi T (2014) Compression stocking length effects on arterial blood pressure and heart rate following head-up tilt in healthy volunteers. Nurs Res 63(6):435–438
94. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK et al (2016) Elastic abdominal binders attenuate orthostatic hypotension in Parkinson's disease. Mov Disord Clin Pract 3(2):156–160
95. Wright RA, Kaufmann HC, Perera R, Opfer-Gehrking TL, McElligott MA, Sheng KN et al (1998) A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. Neurology 51(1):120–124
96. Pathak A, Senard JM (2004) Pharmacology of orthostatic hypotension in Parkinson's disease: from pathophysiology to management. Expert Rev Cardiovasc Ther 2(3):393–403
97. Grubb BP, Samoil D, Kosinski D, Kip K, Brewster P (1994) Use of sertraline hydrochloride in the treatment of refractory neurocardiogenic syncope in children and adolescents. J Am Coll Cardiol 24(2):490–494
98. Lindqvist A, Jalonen J, Laitinen LA, Seppala T, Stromberg C (1996) The effects of midazolam and ephedrine on post-exercise autonomic chronotropic control of the heart in normal subjects. Clin Auton Res 6(6):343–349
99. Hoeldtke RD, Horvath GG, Bryner KD (1995) Treatment of orthostatic tachycardia with erythropoietin. Am J Med 99(5):525–529
100. Biaggioni I, Freeman R, Mathias CJ, Low P, Hewitt LA, Kaufmann H (2015) Randomized withdrawal study of patients with symptomatic neurogenic orthostatic hypotension responsive to droxidopa. Hypertension 65(1):101–107

101. Schoffer KL, Henderson RD, O'Maley K, O'Sullivan JD (2007) Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease. Mov Disord 22(11):1543–1549
102. Senard JM, Rascol O, Durrieu G, Tran MA, Berlan M, Rascol A, et al. Effects of yohimbine on plasma catecholamine levels in orthostatic hypotension related to Parkinson disease or multiple system atrophy. Clinical neuropharmacology. 1993;16(1):70–6.
103. Ramirez CE, Okamoto LE, Arnold AC, Gamboa A, Diedrich A, Choi L et al (2014) Efficacy of atomoxetine versus midodrine for the treatment of orthostatic hypotension in autonomic failure. Hypertension 64(6):1235–1240

Sweating Disorders

4

Walter Struhal and Heinz Lahrmann

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W. Struhal, Dr., PD (✉)
Chair, Department of Neurology, Karl Landsteiner University of Health Sciences, Site Tulln, Tulln, Austria
e-mail: walter.struhal@tulln.lknoe.at

H. Lahrmann
Private office, Vienna 1030, Austria
e-mail: neurologe@lahrmann.at

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4.1 Case Vignette

It all started at the age of 43 years. I noticed increased sweating, interestingly mainly on my trunk. When I had to talk to people, I felt embarrassed about my wet shirt. In my work as a farmer in an alpine area, I did not care too much about it. However, in summer time, it occurred more and more often, that I felt dizzy during hot weather. Over the years sweating increased tremendously and my shirts were always soaked wet. The skin area, that did sweat, however diminished and was lately only an area of about 45 cm of diameter at my chest and back. The winter times in the alps are rough and when it got cold, I felt totally well. In summer time however, dizziness at work and sweating got worse. I went to a hospital and was treated with stellatum blockade. That did in fact stop my sweating but dizziness in the heat exaggerated and I could not work anymore, also at moderate temperatures. So I had to stop my work.

During last summer I had to go to my house and lie down on the kitchen floor. The tiles were pleasantly cool and my dizziness ceased as my body temperature went down. I am worried, because nobody can tell me, what's going on with me.

The patient was seen by a neurologist who noted bilateral pupillotonia and generalised and symmetric hyporeflexia, and a Ross syndrome was diagnosed [8].

4.2 Sweating

Sweating is caused by two different mechanisms: thermoregulation to dissipate heat and emotional sweating. Sweating disorders have to be regarded as severe burden for the patient and eventual medical risk. Excessive sweating is a social problem and mounts into occupational restriction and/or social avoidance behaviour. However, loss of sweating eventually leads to exhaustion, heat stroke or death.

Disorders of sweating (hypo- or hyperhidrosis) can be focal or generalised and appear quite frequently in ANS failure. Evaluation of sudomotor function can provide early diagnosis of small fibre neuropathy [3], particularly in early diabetes mellitus, and is used to provide a measure of cholinergic sympathetic function.

Abnormal sweating results from a wide variety of medications that affect the sympathetic nervous system, the thermoregulatory network or the sweat glands. Furthermore, it may result from sleep-stage disturbances, autonomic nervous system disorders, medullary and spinal cord abnormalities, reduction in serum osmolality or abnormalities of osmoreceptor function, hypercapnia, disorders of hormone secretion (hypothyroidism, postmenopausal syndrome, cortisol) and direct sweat gland stimulation by pressure, heat, trauma or toxins. The key to successful diagnosis of sweating disorders is to differentiate whether the patient suffers hypohidrosis or hyperhidrosis and whether the disorder is focal or generalised.

4.3 Patient's History

In patients, who suffer from sweating disorders, the first approach is to interrogate the subjective disease burden. This will provide the physician with a hint on how extensive clinical investigations and therapeutic interventions need to be.

As mentioned above, the first diagnostic key is whether the dysfunction is focal or generalised. In increased and generalised sweating (i.e. observed on the complete body surface), the patient is suffering hyperhidrosis. The same is true if sweating is absent and generalised. It becomes tricky in increased focal sweating. Does the patient suffer focal hyperhidrosis, or – as in our case vignette – does he suffer compensatory sweating? And in fact the clinical correlate is hypohidrosis in all other regions.

Patients often complain of excessive sweating in warm environment and in emotional or stressful situations (generalised, in certain body regions, or focal), heat intolerance, fatigue and exercise intolerance. Gustatory sweating is a normal phenomenon in most people eating heavily spiced foods and occurs bilaterally focused on scalp and face areas. Unilateral occurrence in contrast is pathologic and may not depend on the type of food. It occurs after parotid surgery and post-traumatic misinnervation of parasympathetic fibres in efferent sympathetic postganglionic neurons innervating sweat glands and blood vessels.

Current medication (Table 4.1) and illnesses (thyroid, gastro-oesophageal reflux, tuberculosis, heart failure, chronic pain, malignancies) have to be interrogated as they may influence sweating. Acute or chronic alcohol and drug intake or withdrawal have a significant effect on sweating.

Table 4.1 Drug-induced hyperhidrosis

Drug class	Common examples	Mechanism
Anticholinesterases	Pyridostigmine	Cholinesterase inhibition
Antidepressants: selective serotonin reuptake inhibitors	Citalopram	Serotonergic effect on the hypothalamus or spinal cord
	Duloxetine	
	Escitalopram	
	Fluoxetine	
	Fluvoxamine	
	Mirtazapine	
	Paroxetine	
	Trazodone	
	Venlafaxine	
Antidepressants: tricyclics	Amitriptyline	Norepinephrine reuptake inhibition with stimulation of peripheral adrenergic receptors
	Desipramine	
	Doxepin	
	Imipramine	

Table 4.1 (continued)

Drug class	Common examples	Mechanism
	Nortriptyline	
	Protriptyline	
Antiglaucoma agents	Physostigmine	Physostigmine = cholinesterase inhibition
	Pilocarpine	Pilocarpine = muscarinic receptor agonism
Bladder stimulants	Bethanechol	Muscarinic receptor agonism
Opioids	Fentanyl	Histamine release
	Hydrocodone	
	Methadone	
	Morphine	
	Oxycodone	
Sialogogues	Cevimeline	Muscarinic receptor agonism
	Pilocarpine	

From Cheshire and Freeman [13]; Cheshire and Fealey [12]

Table 4.2 Questions that may help

Do you sweat in the feet? Are your socks drenched after sports?
Do you sweat in intimate area?
Is there excessive sweating in your armpits?
Did you let things fall down because of sweating in your hands?
Do you feel embarrassed when shaking hands because of sweat sometimes?

Important questions comprise duration of the disorder, diseases and conditions before onset, progression to other body regions, areas of increased or decreased sweating, symmetry, triggers (increased ambient temperature, physical activity, stress), diurnal sweating and comparison to sweating before the onset of disease. Night sweat can be a real distressing symptom with many different reasons. To investigate if the disorder occurs isolated or as part of a generalised autonomic dysfunction, the other autonomic subsystems should be interrogated (s. Chap. 2). The diligent interrogation of a patient suspected of autonomic dysfunction occasionally reveals the phenomenon of gustatory sweating, that is, profuse sweating associated with the ingestion of food. In Table 4.2, we have listed some questions that may help.

For physiology see Sect. 1.2.2, for history taking see Sect. 2.2.2.1.

4.4 Physical Examination

Complete physical and neurological examinations are mandatory, looking for signs of PNP, myelopathy or Horner's syndrome, plexus brachialis lesion, brain stem affection and/or central lesions. To investigate focal sweating dysfunction at

bedside, it is valuable to investigate the patient undressed in a quiet room with comfortable ambient temperature and watch for sweat droplets and areas of skin discoloration. Hairiness and tropical changes of the skin and nails hint to peripheral nerve involvement. Distribution of sweat droplets shall be documented, particularly in regions of increased sweating: the face, dorsal neck, axillae, palms and soles and inguinal region. Measurement of skin temperature in different body regions, lateralisation and distal versus proximal distribution by infrared surface method are recommended. The investigator feels changes in skin moisture and texture by touching. It is notable if there are obvious sweat stains on the clothing. For total absence of sweating, patients should be observed in hot environment, the absence of sweating in isolated areas or restriction of profuse sweating to the upper body, while sweating in the lower body areas is absent (may hint at ANP in diabetes mellitus). Documentation by a standardised sketch or photography may help for follow-up.

4.5 Horner's Syndrome

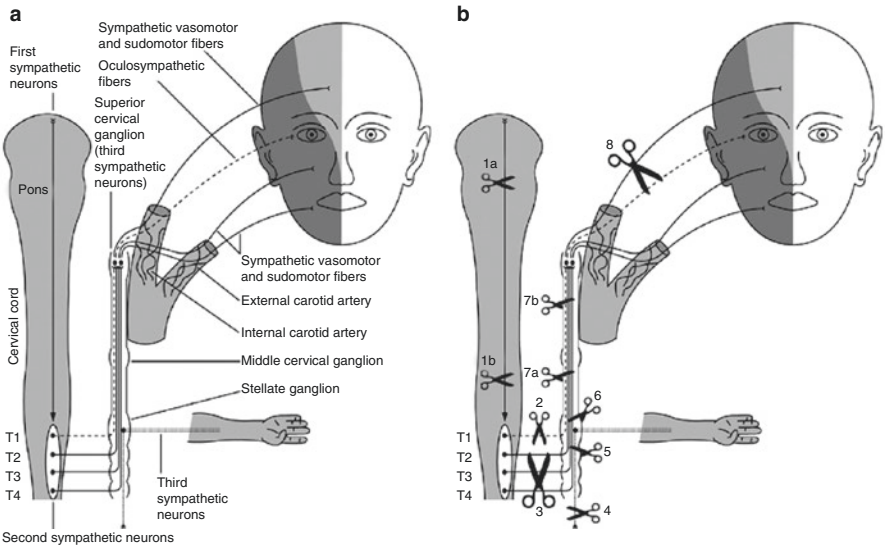
Horner's syndrome (HS) is a central or peripheral sympathetic denervation of the eye. Denervation of the M. tarsalis superior results in ptosis; sympathetic denervation of the inner eye results in parasympathetic predominance causing myosis. HS is best diagnosed in a darkened room. HS is placed in this chapter, because depending on the location of the sympathetic lesion, hypohidrosis occurs to the skin of the forehead/face or ipsilateral arm (Fig. 4.1). Enophthalmus is considered part of the trias. However, enophthalmus per se is only rarely present, being mimicked by ptosis. Therefore a more correct description of HS is:

1. Ptosis
2. Myosis
3. Hypohidrosis

HS is an important hint that – accompanied by other signs – may already help to establish the diagnosis. Clinical evaluation is mandatory along the route of the sympathetic fibres guided by clinical presentation (Fig. 4.1).

HS is also one of the leading signs of *harlequin syndrome*. It is in fact the name of two very different conditions. Here we describe the harlequin syndrome caused by sympathetic lesion; the other condition with this very same name is a skin disorder of congenital ichthyosis.

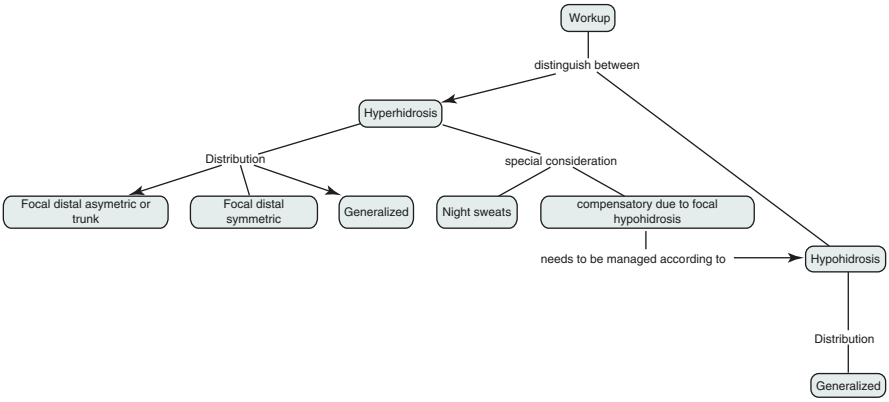
The name is derived from loss of flushing on one side of the face by ipsilateral sympathetic lesion, which prevents sympathetic facial vasodilatation and sweating. The site of the lesion might as well be identified by Fig. 4.1. In rare cases, symptoms of harlequin syndrome are seen in *Adie's syndrome* (tonic pupils with hyporeflexia) or *Ross syndrome* (tonic pupils with hyporeflexia and segmental anhidrosis). The latter two are usually accompanied with a more widespread involvement of the autonomic nervous system.



lesion site	DF	Arm	Horners Syndrome
1	HF	-	central
2	0	=	preganglionic
3	HF	=	0
2+3	HF	=	preganglionic
4	0	-	0
5	HF	-	0
6	HF	-	preganglionic
7	HF	=	preganglionic
8	MFHN	=	postganglionic

Fig. 4.1 Schematic sketch and table helping to diagnose the location of a sympathetic lesion often including Horner's syndrome (Adapted from Wasner et al. [14]); *DF* areas of disturbed facial flushing, *Arm* sympathetic arm innervation, *hf* hemifacial, * medial forehead and nose

4.6 General Considerations for Diagnostic Work-Up



Specific laboratory work-up is necessary only in rare cases and laboratory tests are not widely available [7]. Diagnosis of patients suffering sweating dysfunctions should not depend on the presence of a specialised autonomic laboratory Table 4.1.

4.6.1 Generalised Hyperhidrosis

A carefully taken history should already reveal the generalised character of sweating. In many cases, the patient will tell that "his whole body is soaked wet all the time". It can be time consuming to find out if increased sweating always affects the whole body or only specific areas. What are the exact circumstances and situations when profuse sweating occurs (physical activity, emotional stress, hot environment, night sweat)? How was sweating before the patient noticed the changes, and was there increased focal sweating before? Concomitant diseases, medication and drug abuse have to be evaluated carefully. According to the obtained information, further diagnostic work-up and management have to be planned.

4.6.2 Generalised Hypohidrosis

This is a rare and sometimes life-threatening condition, because of hyperthermia or heat-related illness, as body core temperature homeostasis cannot be maintained. Most patients remain unaware of hypohidrosis and may report on heat intolerance with dizziness, vertigo, dyspnoea and even fainting. It has to be differentiated if the condition increased gradually, maybe as a severe form of progressive hypohidrosis beginning in the extremities, or if it had sudden onset. In the latter case, drugs may play a causal role including antimuscarinic anticholinergic agents, carbonic anhydrase inhibitors and tricyclic antidepressants [12]. These drugs are quite often found to cause sudomotor side effects in elderly patients. Other neurological side effects such as overactive bladder, neuropathic pain, irritable bowel syndrome, reactive airway disease, Parkinson's disease, dizziness, depression, nausea and headache may contribute to heat-associated illness in this population (for a detailed description of the route of action of different drugs, see Cheshire and Fealey [12]). Further factors include decline in sweating responses with ageing and fluid restriction. As acetylcholine is the principal neurocrine mediator, anhidrosis is one of the clinical hallmarks by which acute anticholinergic toxicity may be recognised. The symptom of dry-mouth often accompanies the less apparent symptom of hypohidrosis. In any case, drug screening may be valuable including a drug history, eventually also drug abuse.

4.6.3 Focal Distal Symmetric Hyperhidrosis

This disorder may be easily interrogated from patients. In many cases, focal distal symmetric hyperhidrosis occurs in the course of some other neurological disorders. Chronic alcoholic patients often present with hyperhidrosis in the feet and

sometimes palms [10]. Some of these patients will report on soaked socks. If no other cause for a secondary hyperhidrosis is known, diagnostic management will proceed as delineated in primary hyperhidrosis. Distal hyperhidrosis as generalised hyperhidrosis may cause severe social embarrassment leading to avoidance behaviour. Secondary social and psychological consequences of the disease increase disease burden. Even more, especially plantar hyperhidrosis is eventually causing bromhidrosis (foul-smelling sweat), infection and secondary skin lesions.

4.6.4 Focal Distal Asymmetric or Trunk Hyperhidrosis

This particular form of sweat disorder is often the presentation of a partial hypo- or anhidrosis with compensatory sweating in the preserved body areas. For example, compensatory sweating may be observed in the upper body or trunk and facial region, due to reduced sweating in extremities. However, patients will much more likely notice the sweating than the hypohidrotic areas. In these cases, the distribution and degree of sweat disturbance have to be evaluated carefully and documented for follow-up investigations. To screen for a secondary sweating disorder, other neurological signs are providing valuable hints.

4.6.5 Secondary Hyperhidrosis

Spinal cord injury causing autonomic dysreflexia frequently induces secondary hyperhidrosis, which can occur years after the injury. A number of drugs induce hyperhidrosis (see Table 4.1). Biochemical agents including chemical warfare and pesticides are a rare but not neglectable cause. In addition, other conditions, e.g. hypoglycaemia, anxiety and menopause, induce hyperhidrosis.

Paroxysmal sweating: Neurologic diseases including diencephalic epilepsy, pontine ischaemia and carcinoid syndrome lead to episodes of sweating. Endocrinologic causes for paroxysmal sweating are thyrotoxicosis, which might well respond to beta-blocker and diabetes mellitus. In pheochromocytoma, excess catecholamines lead to recurrent sweating episodes.

4.6.6 Night Sweats

Night sweats are symptoms commonly linked to menopause, tuberculosis and lymphoma. However, night sweats are often reported by persons without these conditions. Other important differential diagnoses include human immunodeficiency, infectious diseases, endocarditis, gastro-oesophageal reflux disease (GORD), sleep-associated breathing disorders (obstructive and central sleep apnoea syndromes and nocturnal hypercapnia in neuromuscular patients with respiratory failure, as observed by one of the authors), hyperthyroidism, hypoglycaemia, later stages of PD, MSA, depression and anxiety disorders (C: medication induced!). A more complete list is presented in Table 4.3. Alcohol use, particularly alcohol dependency and

Table 4.3 Causes of night sweats

Malignancy	Lymphoma
	Leukaemia
	Other neoplasms
Infections	Human immunodeficiency virus
	Tuberculosis
	Mycobacterium avium complex
	Infectious mononucleosis
	Fungal infections (histoplasmosis, coccidioidomycosis)
	Lung abscess 2
	Endocarditis
	Other infections
Endocrine	Ovarian failure
	Hyperthyroidism
	Diabetes mellitus (nocturnal hypoglycaemia)
	Endocrine tumours (pheochromocytoma, carcinoid tumour)
	Orchiectomy
Rheumatologic	Takayasu's arteritis
	Temporal arteritis
	Others
Obstructive sleep apnoea	
Gastro-oesophageal reflux disease	
Chronic fatigue syndrome	
Granulomatous disease	
Chronic eosinophilic pneumonia	
Lymph node hyperplasia	
Diabetes insipidus	
Prinzmetal's angina	
Anxiety	
Depression	
Pregnancy	
Drugs	
Antipyretics (salicylates, acetaminophen)	
Antihypertensives	
Phenothiazines	
Substances of abuse	Alcohol, heroin
Over-bundling	
Autonomic overactivity	

Modified from Viera et al. [15]

acute withdrawal, may cause night sweats. Overall, the prevalence estimates ranged from 10% among older primary care patients to 60% among women on an obstetric inpatient unit [9]. However, some individuals may be less tolerant of either sweat or its cooling effect or anxious about symptoms, like night sweats, that might indicate illness [9].

Management After exclusion of all treatable disorders as causative factors, patients should be assured of the benign character of the disorder, and possible behavioural and environmental measures can be discussed that may help to relief their bothersome symptoms. Alpha-adrenergic blockers may reduce night sweats in patients taking serotonin reuptake inhibitors.

4.6.7 Differentiating Hyperhidrosis from Hypohidrosis with Compensatory Sweating

It may be tricky to differentiate compensatory hyperhidrosis from primary focal hyperhidrosis. Compensatory hyperhidrosis – as mentioned above – occurs in the skin areas, which are less affected in those patients who have severe hypohidrosis in a wide area of their bodies, which might be unnoticed by the patient. There are a number of techniques to investigate the function of the sweat glands (QSART, TRST) or epiphenomena of sweating (e.g. SSR); however, if those are not available, it might be helpful to wrap the patient into a white blanket in an environment of increased temperature, eventually having the patient drink hot tea. Areas which do not sweat will leave no stains on the blanket.

4.6.8 Sweating Disorders Associated with Other Diseases

Sweating disturbances are common (64%) and distressing symptoms in PD that are related mainly to autonomic dysfunction, off periods and dyskinesias [16]. Hyperhidrosis may occur in association with wearing-off phenomena. Compensatory hyperhidrosis may be observed in the upper body, due to reduced sweating in extremities (unlike MSA). PD is characterised by a length-dependent involvement of postganglionic sudomotor fibres, whereas MSA is characterised by widespread, early and preganglionic autonomic failure. In diabetic ANS, length-dependent hypohidrosis may be observed, thus beginning in the soles and palms. Also gustatory sweating may occur in PD patients.

4.7 Laboratory Investigations

Laboratory tests can assess central and peripheral sudomotor function, as the thermoregulatory sweat test (TST, [1]), or postganglionic function alone, the quantitative axon reflex test (QSART, [4]), the sympathetic skin response test (SSRT), the

quantitative direct and indirect axon reflex test (QDIRT, [2]) and the dynamic sweat test (DST, [5]) [6].

TST The test is performed in a temperature- and humidity-controlled chamber (45–50 °C). The whole body is covered with an indicator dye and the changes in colour due to sweat production are documented. Asymmetric patterns due to focal anhidrosis or stocking and glove distributions in length-dependent neuropathy may be observed.

QSART This test measures postganglionic axon reflex-mediated sweat production in a small restricted area of the skin. A multicompartmental sweat capsule is used to stimulate sweat glands by iontophoresis of acetylcholine. A first, direct sweat response in the area of iontophoresis is discriminated from the indirect, axon reflex-mediated response in the surrounding area (e.g. see [3] for details). See Fig. 1.4 for a schematic sketch on how this test works.

SIT The test evaluates postganglionic sympathetic cholinergic sudomotor function by measuring the direct and axon reflex-mediated sweat response. Sweat glands are stimulated by iontophoresis of acetylcholine, pilocarpine or methacholine, followed by application of a thin layer of mouldable material on the skin. Sweat droplets displace the silicone material during polymerisation resulting in permanent impressions that can be quantified by various methods. A number of droplets, size and distribution are reported.

QDIRT and DST These methods quantify sudomotor function with spatial and temporal resolution. They combine the stimulation of sweat glands and sudomotor axons by iontophoresis of a cholinergic agonist into the skin with the colour change of an indicator as sweat pours out. Each sweat droplet results in a colour spot which increases in perimeter and number over time. The evolving pattern of spots is recorded by high-resolution digital photography or video and evaluated with automated image analysis software.

SSRT This neurophysiologic measure of electrodermal activity provides a surrogate marker of sympathetic cholinergic sudomotor function. An arousal stimulus (electric, acoustic, deep breath) induces a change in skin potential, which is recorded from the palms and soles of the feet most often. SSRs are reported as present or absent. For amplitude and latency, normative values have been published.

4.8 Management

4.8.1 Nonpharmacological

Avoid spicy foods, coffee, tea, nicotine and alcohol.

Supporting measures are diverse relaxation techniques (e.g. progressive muscle relaxation).

4.8.2 Treatment of Hypohidrosis

If generalised hypohidrosis is of clinical relevance and drug induced, a reduction of the inducing drug should be considered. Deficient sweating may further be managed by avoiding situations of heat stress and cooling the skin with externally applied water.

4.8.3 Treatment of Hyperhidrosis

Treatment of first choice is topical applications of aluminium salts. Those are already added in many antiperspirant agents; however, a higher dose is necessary in hyperhidrosis (15–25%) several times a day. Side effects include skin irritation and dysaesthesias. Patients should take care not to get in contact with dark clothing directly after application due to discoloration of their clothes. In Frey syndrome, e.g. after surgery, topical application of 0.5% glycopyrrolate is recommended.

Tap water iontophoresis is very effective in palmar and plantar hyperhidrosis. Standard settings are continuous direct current or eventually pulsed direct current, which might be slightly less effective [11]. Patients with implanted pacemakers and pregnant women should abstain from this therapy. Side effects include skin irritations including erythema, blistering and local burning sensations.

If the previous measures were not able to relieve symptoms, botulinus toxin injection may be considered. The application is intradermal. In many patients, a good effect is seen up to 7 months. When applied in palmar hyperhidrosis, paresis of small hand muscles is often observed.

Sympathectomy of the sympathetic ganglia Th2/Th3 is used foremost in palmar hyperhidrosis. However, compensatory hyperhidrosis might complicate this therapy in the long run. Surgery-related complications include haemothorax, pneumothorax, injury to the thoracic duct and the phrenic nerve and Horner's syndrome. See Text Box 4.1.

Generalised hyperhidrosis is treated with anticholinergic drugs (e.g. methanthelinium bromide (2 × 50 mg/day)). Only few data exists on administration. Side effects of anticholinergic drugs might limit the therapy (urinary retention, constipation, memory impairment, drymouth, reduced accommodation). Alternative treatment options are antidepressants (especially tricyclic antidepressants like amitriptyline, but also paroxetine), beta-blockers or calcium channel antagonists (e.g. diltiazem).

Text Box 4.1. Endoscopic Transthoracic Sympathectomy (ETS)

K.A. Leber, Univ. Clinic for Neurosurgery, Medical University Graz

Indication. The classic indication is primary focal axillar and/or palmar hyperhidrosis (HH). Facial blushing, Raynaud's disease, angina pectoris, reflex sympathetic dystrophy and plantar HH are considered as further possible indications. However, the latter is not yet sufficiently documented in literature.

Surgical procedure. ETS is a video-assisted endoscopic keyhole procedure under general anaesthesia. The endoscope is inserted via a single skin incision in the armpit. Through the working channel, a cautery probe is inserted to place two to three thermo-lesions on the sympathetic trunk between ganglia 2, 3 and 4. We also coagulate aberrant, mostly invisible connections up to 3 cm laterally as prevention against recurrences.

Even though the complication rate is fairly low, we operate one side and do the procedure on the other side 6 weeks, thereafter. Instead of thermo-lesions, also cutting is described in literature, or clamping, that can be reversed in case of adverse effects.

Risks and complications. The most common unwanted effect is compensatory sweating on the torso, whereas surgical complications such as infection and bleeding or symptoms from residual pneumothorax are extremely rare.

Results. At the Department of Neurosurgery, Medical University of Graz, we reviewed a total of 44 patients over a period of 60 months. The mean success rate by increased quality of life was 92% (96% for palmar HH and 85% for axillary HH). The recurrence rate was 14%, whereas only two patients required a reoperation. There was no serious complication. Fifty-five percent of the patients reported signs of compensatory HH; however, 18% denoted it onerous, and only one patient (2%) would not have the same procedure again. Compensatory hyperhidrosis was habitually noted temporarily or was accepted in a lesser stage by most of the patients.

Take Home Messages

Sweating disorders:

- Need special considerations.
- Anatomic representation plays a huge role (focal, generalized; hypo-, hyperhidrosis).
- Sweating disorders based on systemic diseases have to be ruled out.
- Non-pharmacological and pharmacological management is available.

References

1. Fealey RD, Low PA, Thomas JE (1989) Thermoregulatory sweating abnormalities in diabetes mellitus. Mayo Clin Proc 64:617–628
2. Gibbons CH, Illigens BMW, Centi J, Freeman R (2008) QDIRT: quantitative direct and indirect test of sudomotor function. Neurology 70:2299–2304
3. Illigens BM, Gibbons CH (2009) Sweat testing to evaluate autonomic function. ClinAuton Res 19(2):79–87
4. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ (1983) Quantitative sudomotor axon reflex test in normal and neuropathic subjects. Ann Neurol 14:573–580

5. Provitera V, Nolano M, Caporaso G, Stancanelli A, Santoro L, Kennedy WR (2010) Evaluation of sudomotor function in diabetes using the dynamic sweat test. Neurology 74:50–56
6. Stewart JD, Nguyen DM, Abrahamowicz M (1994) Quantitative sweat testing using acetylcholine for direct and axon reflex mediated stimulation with silicone mold recording; controls versus neuropathic diabetics. Muscle Nerve 17:1370–1377
7. Lahrmann H, Magnifico F, Haensch CA, Cortelli P (2005) Autonomic nervous system laboratories: a European Survey. Eur J Neurol 12:375–379
8. Ross AT (1958) Progressive selective sudomotor denervation; a case with coexisting Adie's syndrome. Neurology 8:809–817
9. Mold JW et al (2012) Night sweats: a systematic review of the literature. J Am Board Fam Med 25:878–893
10. Tugnoli V, Eleopra R, De Grandis D (1999) Hyperhidrosis and sympathetic skin response in chronic alcoholic patients. Clin Auton Res 9(1):17–22
11. Schlereth T, Dieterich M, Birklein F (2009) Hyperhidrosis—causes and treatment of enhanced sweating. Deutsches Ärzteblatt International 106(3):32–37
12. Cheshire WP, Fealey RD (2008) Drug-induced hyperhidrosis and hypohidrosis. Drug Safety 31(2):109–126
13. Cheshire W, Freeman R (2003) Disorders of Sweating, 23(4):399–406
14. Wasner G, Maag R, Ludwig J, Binder A, Schattschneider J, Stingele R, & Baron R (2005) Harlequin syndrome–one face of many etiologies. Nature Clinical Practice. Neurology, 1(1):54–9. http://doi.org/10.1038/ncpneuro0040
15. Viera AJ, Bond MM, Yates SW (2003) Diagnosing night sweats. American Family Physician, 67(5):1019–24. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12643362
16. Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N (2003) Sweating dysfunction in Parkinson's disease. Movement Disorders: Official Journal of the Movement Disorder Society, 18(12):1459–63. http://doi.org/10.1002/mds.10586

Bladder and Sexual Dysfunction

5

Alessandra Fanciulli, Gusztav Kiss, Sabine Eschlböck, Gregor K. Wenning, and Jalesh N. Panicker

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A. Fanciulli, MD, PhD (✉) • S. Eschlböck • G.K. Wenning
Department of Neurology, Innsbruck Medical University,
Anichstrasse 35, A-6020 Innsbruck, Austria
e-mail: alessandra.fanciulli@i-med.ac.at

G. Kiss
Department of Urology, Innsbruck Medical University, Innsbruck, Austria

J.N. Panicker
The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology,
Queen Square, London, UK

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5.1 Which Clinical Signs Hint at a Urogenital Autonomic Disease?

5.1.1 Neurogenic Bladder Dysfunction

Urinary function consists of a "storage" phase, in which tonic activation of urethral sphincter muscle occurs and bladder detrusor muscle is inhibited, and a "voiding" phase, in which detrusor activation and sphincter relaxation favor passing of urine. Both are under voluntary and involuntary neural control. Disorders of neural control of urinary function are also known as "neurogenic bladder" or "neurogenic lower urinary tract dysfunction." Four main clinical pathological patterns can be distinguished at examination, with different therapeutic implications [41]:

1. Bladder detrusor overactivity: bladder storage capacity is reduced, but no or only low urine post-void volume occurs.
2. Detrusor sphincter dyssynergia: bladder storage capacity is reduced. Lack of coordination between bladder detrusor activation and urethral sphincter relaxation additionally induces post-void residual urine.
3. Hypoactive bladder: bladder capacity is increased. Insufficient detrusor activation leads to high post-void residual urine.
4. Hypoactive sphincter: bladder storage capacity is reduced, with no post-void residual urine.

For all purposes, peripheral nerve palsies cause hypoactive bladder and hypoactive sphincter, while central lesions (i.e., above the S2–S4 spinal micturition center) cause detrusor and sphincter overactivity and additionally detrusor sphincter dyssynergia, if the lesion is located at suprasacral spinal level.

For anatomy, see Sect. 1.2.

5.1.1.1 History Taking

When evaluating a patient for neuro-urological complaints, mental status, physical mobility, as well as comorbidities, symptomatic burden and treatment expectations need to be taken into account to establish a tailored therapeutic approach. In multiple system atrophy (MSA), for example, male patients may undergo futile prostatic or bladder neck surgery before the correct diagnosis is assessed [3]. Similarly, stress incontinence occurs in the majority of female MSA patients, but surgical procedures, if applied, have proven futile [3, 6].

For further details on history taking see Sect. 2.2.3.

5.1.1.2 Physical Examination

Urinary retention, frequency, as well as urgency and nocturia may be caused or exacerbated by benign prostatic hypertrophy in men or by perineal laxity secondary to multiple parity or pelvic organ prolapse in women. Masses, relevant surgical scars, and prolapses are frequent confounders or exacerbating factors, which need to be ruled out, or documented, at the first evaluation.

5.1.1.3 Urine Dipstick

Urinary tract infections, though developing more frequently in patients with neurogenic bladder, can also cause or exacerbate urinary complains and need to be ruled out or, eventually, treated prior to assessment of symptomatic burden.

Furthermore, if repeated urine dipstick suggests micro- or macrohematuria, further investigation (i.e., cystoscopy, abdominal CT) is warranted to exclude expanding lesions.

5.1.1.4 Bladder Diary

A "bladder diary" is a simple, cost-effective tool, through which urine frequency, volume, as well as difficulties in initiating or suppressing voiding, and episodes of urinary incontinence during day- and nighttime can be recorded. A bladder diary template is provided in Fig. 5.1. Completing a bladder diary over at least 2 days is essential to document symptoms' severity, their distribution over the 24 h, plan individualized interventions, and, later on, monitoring for therapeutic outcome.

The complete diagnostic work-up of urological autonomic failure is summarized in Fig. 5.2.

5.1.1.5 Investigations

Post-void urine volume can be assessed by means of in-out catheterization or, non-invasively, by bladder ultrasound. Uroflowmetry is particularly indicated in men: in case of reduced urine flow, prostatic enlargement needs to be excluded.

The gold standard for a detailed evaluation of urinary storage and/or voiding dysfunction in patients with suspected neurogenic bladder is the urodynamic evaluation. Sterile urine is a prerequisite for performing this examination safely and minimizing the risk of pyelonephritis. For detailed description of urodynamic assessment, see Text Box 5.1 "Focus on Neuro-urological Investigations."

Urodynamic assessment includes a multichannel registration, which combines cystometrogram (CMG) with pressure flow study and electromyography (EMG). During the examination, the patient is in his/her usual voiding position. A transurethral and a rectal balloon catheter detect intravesical (Pves) and abdominal pressure (Pabd). Based on measured pressures, detrusor pressure (Pdet) can be calculated (pdet = Pves – Pabd). EMG surface electrodes are used to assess external urethral sphincter activity throughout urodynamic testing. Combination of multichannel urodynamic testing with radiographic imaging, also known as videourodynamic study (or VUDS), provides further morphological information and can be performed in selected cases. Sterile water or saline is used as fluid medium for the bladder filling phase during standard urodynamic evaluation, while Cystografin and fluoroscopy table tilted to 45–60° are used in case of videourodynamic study.

During the filling phase, bladder storage is assessed by asking the patient about sensation of bladder filling and is quantified by means of the bladder wall elasticity (compliance, $C = \Delta V/\Delta$ Pdet). The "leak point pressure," that is, the pressure at which urinary loss is experienced without detrusor contraction, is measured for evaluation of neurogenic bladder and stress urinary incontinence. Voiding

Date	Time	Voided volume	Fluid intake	Urinary leakage
23.05.2017	06.00	450 mL		No
	07:00		150 mL	No
	08:00			Yes
	09:00	150 mL		No
	09:30		Coffee (30 mL)	
	…			
	…			

Fig. 5.1 Template of a bladder diary, complete over at least 48 hrs

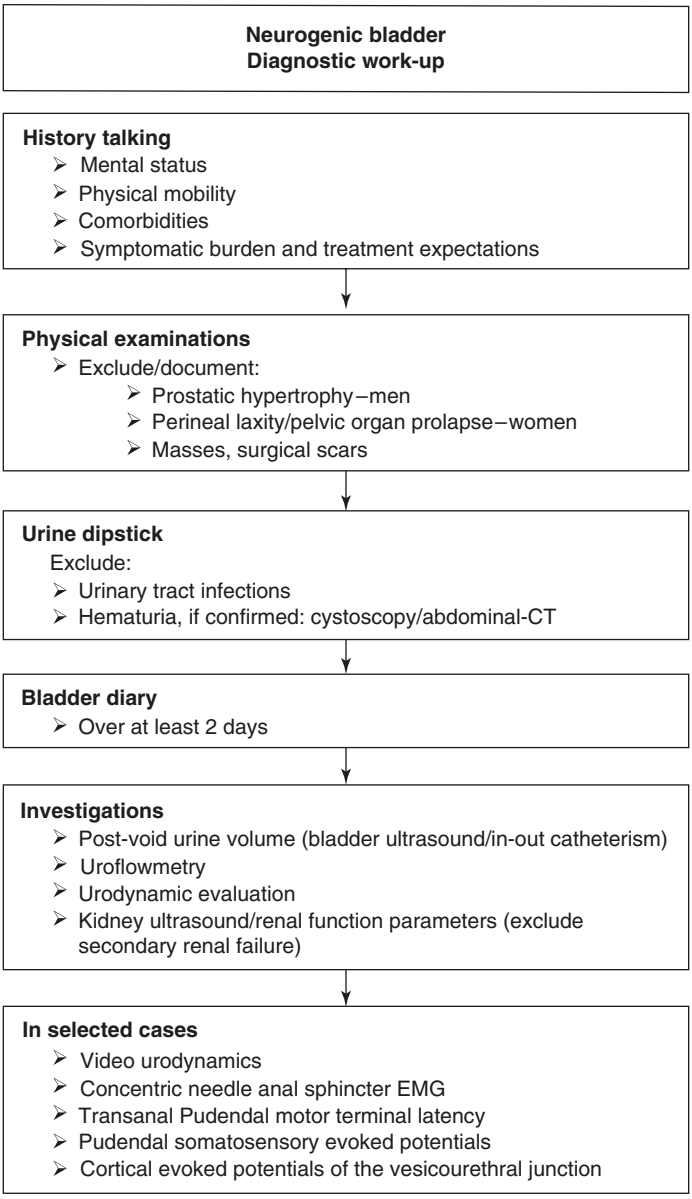

Fig. 5.2 Neurogenic bladder: diagnostic work-up

dysfunction, including detrusor sphincter dyssynergia, is detected via EMG, and urine evacuation is quantified by pressure flow study recording flow rate, voided volume, and related pressures (Pabd, Pves, Pdet). Provocative maneuvers including cough or Valsalva maneuver may be performed to elicit detrusor overactivity and to unmask stress urinary incontinence [31].

Kidney ultrasound and functional renal assessment (creatinine clearance and blood urea) are recommended to exclude, or eventually monitor for, hydronephrosis, reflux, and secondary renal failure.

Electrophysiological studies may be added in single cases (see Text Box 5.1).

Text Box 5.1 Focus on Neuro-urological Investigations

Urodynamic assessment: it includes a multichannel registration, which combines cystometrogram (CMG) with pressure flow study and electromyography (EMG). During the examination, the patient is in his/her usual voiding position. A transurethral and a rectal balloon catheter detect intravesical (Pves) and abdominal pressure (Pabd). Sterile water or saline is used as fluid medium for the bladder filling phase. Based on measured pressures, detrusor pressure (Pdet) can be calculated (pdet = Pves – Pabd). EMG surface electrodes are used to assess external urethral sphincter activity throughout urodynamic testing. Bladder storage capacity is assessed by asking the patient about sensation of bladder filling. The "leak point pressure," that is, the pressure at which urinary loss is experienced without detrusor contraction, is measured for evaluation of neurogenic bladder and stress urinary incontinence. Voiding dysfunction, including detrusor sphincter dyssynergia, is detected via EMG, and urine evacuation is quantified by pressure flow study. Provocative maneuvers including cough or Valsalva maneuver may be performed to elicit detrusor overactivity and to unmask stress urinary incontinence [31].

Videourodynamic assessment: based on the combination of multichannel urodynamic testing with radiographic imaging, it provides further morphological information and can be performed in selected cases. In this case, Cystografin and a fluoroscopy table, tilted to 45–60°, are used.

- *Concentric needle anal sphincter electromyography (EMG)*: can be used to investigate muscle reinnervation following axonal damage to the sacral spinal segments S2–S4. In the setting of suspected neurodegenerative disorders, the test is useful to evaluate the integrity of the motor neurons of these segments, known as Onuf's nucleus. Neuronal loss in Onuf's nucleus is a characteristic, but not exclusive, feature of MSA, therefore limiting the role of this investigation in the differential diagnosis of parkinsonian syndromes [26, 34, 35, 42, 45, 47].
- *Transanal pudendal motor terminal latency*: may help to evaluate a distal lesion of pudendal motor fibers.
- *Pudendal somatosensory evoked potentials*: to investigate for lesions of pudendal somatosensory afferent fibers.
- Cortical evoked potentials of the vesicourethral junction: evaluate viscerosensory afferent pathways in patients with lower urinary tract dysfunction. Combined with evaluation of pudendal somatosensory evoked potentials, it distinguishes between intraspinal and extraspinal (e.g., sacral plexus) lesions of the bladder afferent pathways, if the site of lesion is unknown [22].

5.1.2 Sexual Dysfunction

Male erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [7]. Prevalence of ED is 2% in the third decade of life and may increase up to 53% in the seventh decade [5].

ED may be of organic, psychogenic, or, in most of cases, multifactorial origin. A psychogenic cause is suspected in case of sudden onset, previous or ongoing stressful events, situation-dependent disturbs (contact with a partner versus masturbation), absence of relevant organic risk factors, young age, and preserved spontaneous nocturnal erections. Organic causes of ED encounter vascular origin (arterial, venous, or mixed), structural penile abnormalities, and endocrine or neurogenic causes. Erectile dysfunction may be the presenting feature of primary autonomic disorders like multiple system atrophy [13] and pure autonomic failure [1], frequently occurs in patients with spinal cord injuries [44] and multiple sclerosis [25], and may complicate diabetes mellitus or polyneuropathies of diverse etiologies.

History taking is essential for a proper diagnostic work-up of erectile complaints: even if a putative cause for ED is suspected (e.g., previous diagnosis of polyneuropathy), a careful history taking should be aimed at pointing out further, eventually modifiable, contributing factors. Patients' psychosocial, lifestyle, and pharmacological aspects, as well as comorbidities, should be taken into account during the first diagnostic assessment (see also Table 5.1 – *History taking in males referring erectile dysfunction*). Sexual anamnesis should be carefully documented, if possible

Table 5.1 History taking in patients referring erectile dysfunction

Comorbidities	Arterial hypertension Hyperlipidemia Diabetes mellitus (for both vascular and neurogenic erectile dysfunction) Depression Parkinsonism Multiple sclerosis Polyneuropathy of any etiology Spinal stenosis Hyperprolactinemia Hypothyroidism Hypogonadism Obesity
Risk factors	Smoking Sedentary lifestyle Increased alcohol intake Recreational drug use (e.g., cocaine, by inducing hyperprolactinemia) Previous pelvic or perineal surgery, trauma, or radiotherapy
Drugs	Thiazide type diuretics Aldosterone receptor blockers β-blockers Benzodiazepines SSRI Antiepileptic drugs

also with the bed partner in order to define disease burden and plan tailored interventions. Several rating scales have been developed for research purposes in order to stratify severity degree of male ED: the most frequently used is the "International Index of Erectile Function – 5 items" (IIEF-5 scale), which is reported in Table 5.2 [32] and may be used on a routine basis for follow-up purposes as well. In case a

Table 5.2 The IIEF-5 questionnaire

Over the past 6 months:	1	2	3	4	5
1. How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never	A few times (much less than half the time)	Sometimes (About half the time)	Most times (much more than half the time)	Almost always/ always
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never	A few times (much less than half the time)	Sometimes (About half the time)	Most times (much more than half the time)	Almost always/ always
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always

Reprinted from Rosen et al. [32], with permission from the Nature Publishing Group
The IIEF-5 questionnaire is the sum of the ordinal responses to the five items (range, 5–25)

psychogenic ED is suspected, a multidisciplinary evaluation, including psychopathological assessment, is recommended.

Physical examination of the abdomen, penis, testicles, secondary sexual characteristics, and leg arterial pulses should be performed at first visit. Digital rectal examination of the prostate and serum PSA are recommended in men above 40 years of age: this is particularly important in case ED is due to hypogonadism and testosterone replacement therapy is planned.

Laboratory testing is also recommended at first visit and should include blood glucose, HbA1c, HDL and LDL cholesterol, liver enzymes, creatinine, and blood count. In patients with gynecomastia, androgen hormone measurement should be also performed.

Provocative erection test (intracavernous prostaglandin E1 injection – Alprostadil), alone or in combination with Doppler ultrasound, can be considered if penile artery disease is suspected. In case of penile arteriopathy, further investigations should be prompted to exclude an ongoing coronary artery disease.

Electrophysiological studies can be considered if a neurogenic cause of ED is suspected. Autonomic ɣ-fibers inducing vasodilation of cavernous vessels cannot be tested, but anal sphincter electromyography, pudendal nerve terminal motor latency, and somatosensory evoked potentials of pudendal nerve may provide indirect clues for a neurogenic etiology in unclear cases (Fig. 5.3).

In women, sexual dysfunction may manifest with decreased vaginal lubrication and dryness, anorgasmia, and low sexual drive. Any kind of lesion affecting neural pathways subserving sexual function may cause neurogenic sexual dysfunction, but like in men, a multifactorial origin is more often the case, with both organic and psychosocial aspects playing a key role (see above). In particular, age- or delivery-related perineal laxity, endocrine changes (i.e., age-related/drug-induced/iatrogenic menopause, contraceptive pill), concomitant bladder or bowel dysfunction, spasticity, or depression may influence libido and sexual function to a great extent. Hence, these aspects need to be considered when evaluating female patients with hypoactive sexual complaints. Questionnaire can be used for initial assessment and follow-up of female neurogenic sexual dysfunction: the most frequently used are the "sexual function questionnaire (SFD)" and the "female sexual function index – FSFI" [27].

5.2 Therapeutics of Bladder and Sexual Dysfunction

5.2.1 Neurogenic Bladder Dysfunction

Management of lower urinary tract autonomic dysfunction contemporarily aims at optimizing quality of life, by reducing incontinence episodes and increasing voiding control and protecting upper urinary tract from secondary damage. Therapeutic options need to be individualized, by taking into account objective findings, comorbidities, global health status, and personal expectations of the patient [36].

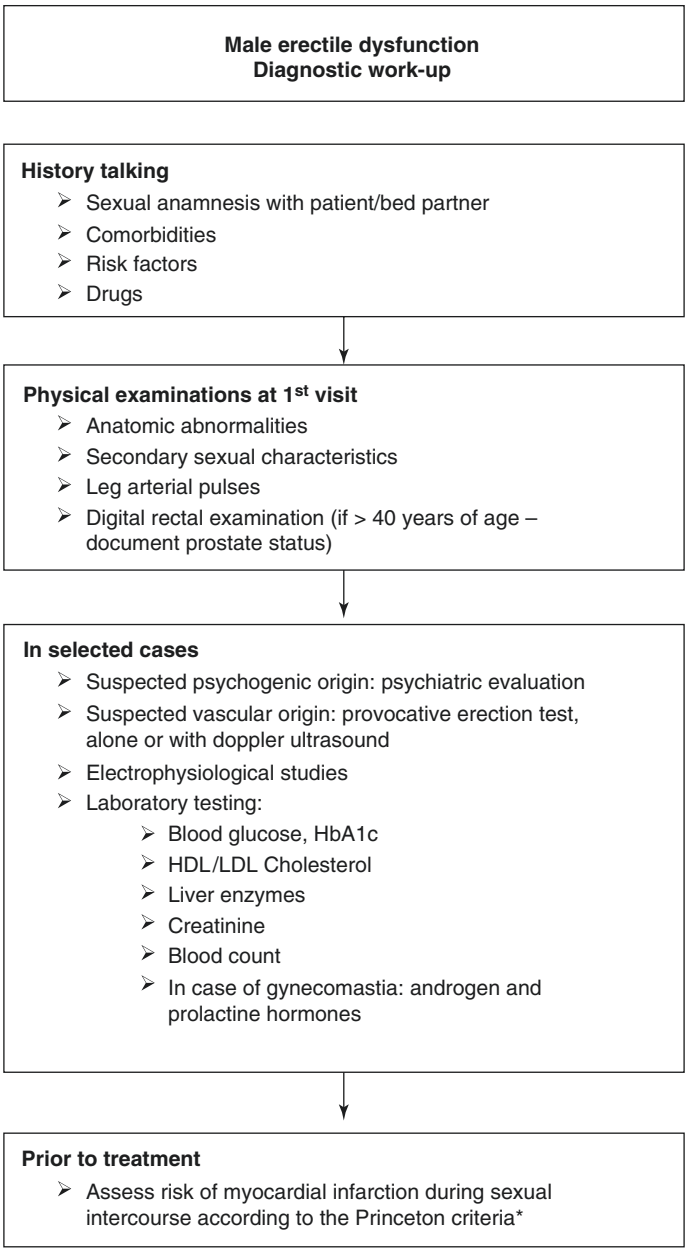

Fig. 5.3 Male erectile dysfunction: diagnostic work-up *[30]

5.2.1.1 Storage Dysfunction

Overactive Bladder

Non-pharmacological treatment of detrusor overactivity by means of bladder training may be pursued in patients with milder symptoms or as add-on to pharmacological measures: patients are trained to resist urge symptoms for a stepwise longer interval until urine volume and frequency do not normalize [46].

Antimuscarinic agents are the first-line therapy for treatment of detrusor overactivity. Oxybutynin, tolterodine, solifenacin, darifenacin, and trospium relieve urge and incontinence. Possible side effects are increased post-void residual volumes, xerostomia, constipation, and blurred vision [48]. Delirium, confusion, and worsening of cognitive impairment are further side effects due to central anticholinergic activity, limiting their use in patients with overt dementia. To this end, trospium, said not to pass the blood-brain barrier, and darifenacin, more selective for the peripheral M3 muscarinic receptor subtype, should induce cognitive side effects less frequently [21, 43]. Four to 6 weeks after beginning an antimuscarinic therapy, therapeutic outcome as well eventual side effects should be monitored. Post-void urine volume should be monitored during the titration phase and after dose changes, as this may rise due to drug-induced hypoactive bladder [2].

In refractory cases, more invasive options can be considered. Botulinum toxin A intravesical injection may reduce incontinence episodes due to detrusor overactivity. The treatment reduces detrusor contractility, impairing voluntary voiding and resulting in urinary retention. Therefore, this procedure is indicated only in patients able to perform clean intermittent self-catheterization and not, for instance, in patients with a severe cognitive of motor impairment [8, 16, 38].

Other invasive options for treatment of therapy-resistant detrusor overactivity include sacral neuromodulation or, in selected cases and depending on disease prognosis and life expectancy, bladder augmentation through partial detrusor myectomy or ileal transplant [24]. Recent evidence suggests that percutaneous posterior tibial nerve stimulation may improve lower urinary tract symptoms and urodynamic findings in patients with Parkinson's disease suffering from overactive bladder [20].

Stress Incontinence

Conservative measures for treating stress incontinence due to hypoactive sphincter and/or pelvic floor laxity include pelvic floor training and behavioral therapy by means of biofeedback [17]. Invasive procedures include implantation of an artificial urethral sphincter [11, 15] or, in single cases, transurethral infiltration with bulking agents (i.e., fat, collagen, silicon, Teflon) but are to be considered on the basis of the patient's life expectancy.

Nocturia

In patients reporting nocturia, it is essential to distinguish, on the basis of the bladder diary records, whether this is due to (I) increased nocturnal urine output (i.e., more than 1/3 of the 24 h total urine volume is excreted overnight, e.g., in case of pressure natriuresis in patients affected by nocturnal hypertension), (II)

generally increased urine output (>40 mL/kg body weight, e.g., in case of uncontrolled diabetes), and (III) reduced bladder capacity (e.g., in case of overactive bladder). A combination of more than one cause is frequent, and a number of other contributing factors need to be taken into account at first evaluation. These are uncontrolled arterial hypertension with nocturnal blood pressure rise, diuretics scheduled in the evening, sleep apnea, psychogenic polydipsia, and insufficient antidiuretic hormone secretion (either idiopathic, drug-induced, or due to neuropituitary lesions).

For non-pharmacological treatment of nocturia, patients should be advised to limit their water intake in the late afternoon/evening, avoid evening alcohol consumption, and sleep in a 30° head-up tilt position [40]. Pharmacological treatment with desmopressin at bedtime may be indicated in patients with increased nocturnal urine output, but monitoring for blood pressure, serum electrolytes, and body weight changes is mandatory [33]. Bedtime administration of antimuscarinic agents is indicated in patients with reduced bladder capacity as cause for nocturia.

5.2.1.2 Voiding Dysfunction

Detrusor Sphincter Dyssynergia

Clean intermittent self-catheterization is the treatment of choice for patients with urinary retention and post-void urine residuum >100 mL. Frequency of catheterization is to be tailored according to urodynamic findings and post-void volume. For practical purposes, it is suggested to perform one catheterization per day for every 100 mL of urine residual volume (e.g., if residual volume is 300 mL, then catheterism thrice daily) [19, 48]. Remarkably, this approach may cause urethral ulceration on the long term, fail to prevent from recurrent urinary tract infections, or result impracticable in patients with severe motor impairment (e.g., multiple system atrophy), so that suprapubic indwelling catheterization may turn necessary over time. Add-on pharmacological therapies for urinary retention are either designed to enhancing vesical detrusor contractility (cholinergic agents) or promoting urethral smooth sphincter relaxation (α_1-adrenoreceptor antagonists) [19].

One study suggested the use of a bladder stimulator as a possible alternative to self-catheterization in selected patients [9]. For refractory cases, surgical options like urethral sphincterectomy, bladder augmentation, or ileal conduit urinary diversion may be considered.

Hypoactive Bladder

In case of hypoactive bladder, treatment with cholinergic agents (e.g., bethanechol) or α_1-adrenoreceptor antagonists may be pursued [19]. Remarkably, α_1-adrenoreceptor blockers should be prescribed cautiously in patients with neurogenic orthostatic hypotension, due to exacerbation of this latter under treatment with α_1-adrenoreceptor blockers. Tamsulosin may be preferred in this case, given a higher selectivity for prostatic α_1-adrenoreceptors [37]. Evening scheduling is also suggested in order to minimize hypotensive side effects. In case of post-void urine

residuum >100 mL, clean intermittent catheterism or, if unfeasible, suprapubic indwelling catheterization is suggested in order to prevent the upper urinary tract from retrograde damage.

5.2.2 Sexual Dysfunction

5.2.2.1 Pharmacological Measures

Eventual comorbidities (e.g., hypogonadism, hyperprolactinemia) should be treated appropriately. Pharmacological measures should be applied stepwise, according to their invasiveness and risk/benefit ratio.

Since ED and cardiovascular diseases often share a common etiology, it frequently happens that patients with ED present with one or more cardiovascular comorbidities, thus limiting therapeutic options. Prior to treatment, patients should be stratified into high, intermediate, and low risk of developing myocardial infarction during sexual intercourse according to the Princeton Consensus Panel [23]. Patients with:

(i) Unstable or refractory angina
(ii) Uncontrolled hypertension
(iii) Congestive heart failure
(iv) Myocardial infarction in the previous 2 weeks
(v) High-risk arrhythmias
(vi) Hypertrophic, obstructive, or other cardiomyopathies
(vii) Moderate-to-severe valvular disease

are considered at high risk and should not be treated for ED until the cardiovascular comorbidity is sufficiently treated. To the contrary, patients at low risk of myocardial infarction during sexual intercourse, i.e.,

(i) Asymptomatic coronary disease
(ii) Controlled hypertension
(iii) Mild stable angina
(iv) Mild valvular disease
(v) Uncomplicated stenting

might be considered for all first-line therapies ([23, 30]).

Oral phosphodiesterase (PDE-5) inhibitors are the first-line therapy for ED. These are sildenafil, tadalafil, vardenafil, and avanafil, with no sufficient evidence supporting the superiority of one with respect to the others [28]. Sildenafil proves efficacious in parkinsonian men with ED, by ameliorating both achievement and maintaining of erection, but exacerbation of orthostatic hypotension is a predictable side effect [18]. A precautionary measurement of supine and standing blood pressure is therefore highly recommended before prescribing sildenafil to parkinsonian

patients. Tadalafil, having the longest T_2, is also relative contraindicated in patients suffering from orthostatic hypotension [18]. Attention should be paid in patients taking α_1-adrenoceptor blockers (e.g., tamsulosin for benign prostatic hypertrophy), due to synergistic hypotensive effects. PDE inhibitors should not be prescribed to patients on nitrate therapy.

In case of therapeutic failure, another PDE inhibitor may be tried. Alternatively, intraurethral alprostadil (vasodilatory prostaglandins), alone or in combination with a PDE inhibitor or vacuum constriction, can be considered. Penile erection develops regardless of the subject's will after prostaglandin administration, and possible side effects include priapism, hemorrhages, and infections. Vaginal burning sensation may also occur in the partner. Intra-cavernous vasodilatory prostaglandin administration is a more invasive approach, which can be considered, although associated with a higher risk of priapism and infections: first administration should occur under physician's supervision, and training is recommended to increase therapeutic success.

In a recent meta-analysis, PDE-5 inhibitors resulted effective in treating female sexual dysfunction, with some studies reporting negative results, but incidence of adverse events (headache, flushes, color-vision changes) is a considerable issue. Hormone replacement therapy in peri- and postmenopausal women and bupropion and transdermal testosterone administration have been suggested as off-label therapeutic options in female patients with hypoactive sexual dysfunction, but long-term safety data is controversial [39].

5.2.2.2 Non-pharmacological Measures

Psychological counseling is recommended in case of psychogenic ED. Lifestyle measures, like weight control, quitting smoking, reducing alcohol consumption, and regular exercise may be encouraged in case of organic ED, although level of evidence is low [12]. Mechanical strategies include vacuum constriction and, for therapy-resistant cases, penile prosthesis implantation. Vacuum constriction devices must contain a vacuum limiter to avoid penile injuries. Prosthesis implantation requires appropriate counseling of patient and partner due to risk of infection, erosion, mechanical failure, eventually necessity of reoperation, and loose of residual erectile function if the device is removed [10].

Clitoral vacuum therapy devices (Eros Therapy™) are approved by the FDA for non-pharmacological treatment of female sexual dysfunction, favoring clitoral engorgement, vaginal lubrication, and orgasmic ability [4] (Table 5.3).

Table 5.3 Pharmacological treatment of bladder and sexual dysfunction

Urinary incontinence				
Antimuscarinic agents [48]	Attenuates vesical detrusor overactivity	Darifenacin (7.5–15 mg, o.i.d.) Trospium (60 mg e.r., o.i.d.) Oxybutynin (5 mg, b.i.d./t.i.d.) Tolterodine (2 mg, t.i.d.) Solifenacin (5 mg, o.i.d.)	Increase of residual post-void urine volume, dry mouth, constipation, blurred vision, delirium, confusion, cognitive worsening	Darifenacin or trospium (peripherally acting agents) is preferred, particularly in case of cognitive impairment
Vesical detrusor BoNT type A injection [48]	Attenuates vesical detrusor overactivity	200 U or customized	Increase of residual post-void urine volume	Invasive procedure, requires anesthesia Second choice therapy if lack of responsiveness or tolerability to antimuscarinic agents (FDA recommendation)
Urinary retention				
α_1-Adrenoreceptor antagonists [48]	Induce urethral smooth sphincter relaxation	Tamsulosin (0.4 mg, o.i.d.) Prazosin (1 mg, t.i.d.) Alfuzosin (5 mg, b.i.d.) Terazosin (2–10 mg, o.i.d.) Doxazosin (2–4 mg, o.i.d.)	Worsening of OH, syncope	To be scheduled at bedtime Tamsulosin (selective urethral α_1 adrenoreceptor antagonist) induces less cardiovascular side effects
Muscarinic agents [48]	Increase vesical detrusor contraction	Distigmine chloride (10–15 mg/day) Bethanechol chloride (30–45 mg/day)	Urinary incontinence, drooling, diarrhea, stomach cramps	Investigational use
Nocturia				
Desmopressin [33]	V_2 vasopressin receptor agonist. Promotes water reabsorption from renal collecting ducts, expands plasma volume	5–40 μg o.i.d. (nasal spray) 100–800 μg o.i.d. (oral administration)	Water intoxication, hyponatremia	To be scheduled at bedtime Monitor plasma electrolytes Can ameliorate sleep fragmentation and daytime sleepiness To be coupled with a 10–20° head-up tilt during sleep [14] May also ameliorate daytime OH

(continued)

Table 5.3 (continued)

Nocturia				
Antimuscarinic agents [48]	Attenuates vesical detrusor overactivity	Darifenacin (7.5–15 mg, o.i.d.) Trospium (60 mg e.r., o.i.d.) Oxybutynin (5 mg, b.i.d./t.i.d.) Tolterodine (2 mg, t.i.d.) Solifenacin (5 mg, o.i.d.)	Increase of residual post-void urine volume, dry mouth, constipation, blurred vision, delirium, confusion, cognitive worsening	Administered at bedtime in patients with nocturia caused by vesical detrusor overactivity
Sexual dysfunction				
Sildenafil [18, 28]	Phosphodiesterase-5 inhibitor	50–100 mg on demand	Worsening of OH	No conclusive data in female patients available; possible safety issues in female patients
Alprostadil [29]	Vasodilatory prostaglandin	10–20 μg intracavernous injection on demand	Priapism, hemorrhages, infections	Second choice therapy, but preferable in case of severe OH

Adapted from Fanciulli and Wenning [13], with permission from the Massachusetts Medical Society

5.3 Clinical Case Discussion

5.3.1 Case 1: Urinary Complaints in Relapsing-Remitting Multiple Sclerosis

A 31-year-old female patient, with a history of relapsing-remitting multiple sclerosis and a disease duration of 4 years, complains about urinary urgency, frequency, as well as occasional urinary incontinence.

At neurological examination mild bilateral action tremor and balance disturbances are present. Cerebral and spinal MRI demonstrates lesions within infratentorial and periventricular regions, including the pontine micturition center and the lumbosacral spinal cord segments.

The bladder diary reveals frequency, urgency, and nocturia. Uroflowmetry documents a decreased and interrupted urine flow. Post-void urine residuum is 150 ml. The patient undergoes urodynamic evaluation, which confirms phasic detrusor overactivity as well as a detrusor sphincter dyssynergia (see Fig. 5.4).

Because of neurogenic bladder in the setting of multiple sclerosis, antimuscarinic therapy with tolterodine 2 × 2 mg is initiated, which results in improvement of bladder control without increasing residual urine.

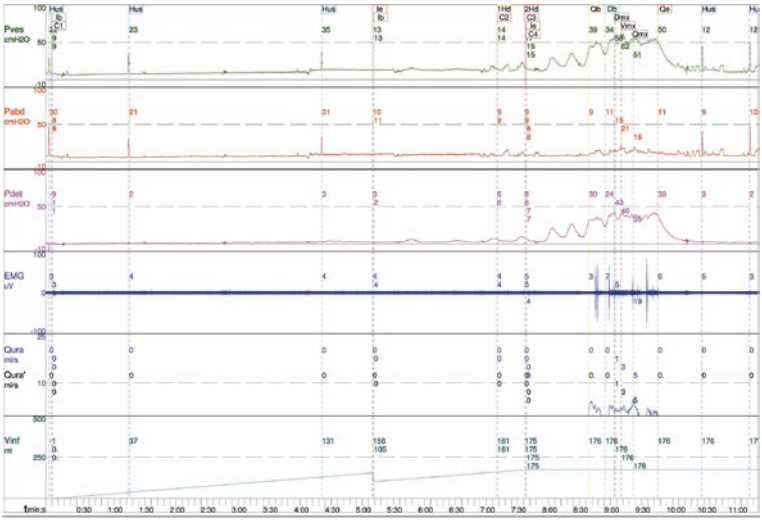

Fig. 5.4 Urodynamic pattern changes in a 31-year-old MS patient. Urodynamic evaluation demonstrates phasic detrusor overactivity during filling phase and detrusor sphincter dyssynergia as well as an interrupted and decreased urine flow during voiding phase. *Pves* vesical pressure, *Pabd* abdominal pressure, *Pdet* detrusor pressure, *EMG* electromyography, *Qura* urine flow, *Vinf* infusion fluid volume, *1Hd* first sensation of bladder filling, *2Hd* second sensation of bladder filling

5.3.2 Case 2: Neurogenic Erectile Dysfunction

A 45-year-old man, who is married and sexually active, complains about severe erectile dysfunction (IIEF-5: 7). Despite sexual desire, achieving and maintaining erection is not possible. The patient suffers from insulin-dependent, inadequately controlled diabetes mellitus for at least 15 years.

Urological and andrological examination gave normal results, but a neurological investigation revealed a marked diabetic neuropathy. Concentric needle anal sphincter EMG reveals diminished activity, and pudendal nerve SSEP shows a prolonged peripheral latency, further supporting the suspicion of a neurogenic erectile dysfunction.

Beside adjustment of blood glucose levels, a phosphodiesterase-5 (PDE5) inhibitor (sildenafil 25–100 mg; 1 h and 30 min prior to sexual activity) is recommended in this case, given assessment of risk of myocardial infarction during sexual intercourse is low according to the Princeton criteria [23, 30].

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References

1. AAN TCCotAat (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology 46(5):1470
2. Alhasso AA, McKinlay J, Patrick K, Stewart L (2006) Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Cochrane Database Syst Rev (4):CD003193
3. Beck RO, Betts CD, Fowler CJ (1994) Genitourinary dysfunction in multiple system atrophy: clinical features and treatment in 62 cases. J Urol 151(5):1336–1341
4. Billups KL, Berman L, Berman J, Metz ME, Glennon ME, Goldstein I (2001) A new non-pharmacological vacuum therapy for female sexual dysfunction. J Sex Marital Ther 27(5): 435–441
5. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U (2000) Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impot Res 12(6):305–311
6. Chandiramani VA, Palace J, Fowler CJ (1997) How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol 80(1):100–104
7. Consensus Development Conference N (1992) Impotence. NIH Consens Statement 10(4): 1–33
8. Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, Daniell G, Heesakkers J, Haag-Molkenteller C (2011) Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol 60(4):742–750
9. Dasgupta P, Haslam C, Goodwin R, Fowler CJ (1997) The 'Queen Square bladder stimulator': a device for assisting emptying of the neurogenic bladder. Br J Urol 80(2):234–237
10. Drogo KM, Jonathan PJ, Gregory AB, Roger RD, Jeremy PWH, Tom FL, Aaron JM, Ajay N, Ira DS (2007) AUA guideline on the management of erectile dysfunction https://www.auanet.org/education/guidelines/erectile-dysfunction.cfm
11. Elliott DS, Barrett DM (1998) The artificial urinary sphincter in the female: indications for use, surgical approach and results. Int Urogynecol J Pelvic Floor Dysfunct 9(6):409–415

12. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D (2004) Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 291(24):2978–2984
13. Fanciulli A, Wenning GK (2015) Multiple-system atrophy. N Engl J Med 372(3):249–263
14. Freeman R (2008) Clinical practice. Neurogenic ort hostatic hypot ension. N Engl J Med 358(6):615–624
15. Fulford SC, Sutton C, Bales G, Hickling M, Stephenson TP (1997) The fate of the 'modern' artificial urinary sphincter with a follow-up of more than 10 years. Br J Urol 79(5):713–716
16. Giannantoni A, Rossi A, Mearini E, Del Zingaro M, Porena M, Berardelli A (2009) Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. J Urol 182(4):1453–1457
17. Hay-Smith EJ, Dumoulin C (2006) Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev (1):CD005654
18. Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ (2001) Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. J Neurol Neurosurg Psychiatry 71(3):371–374
19. Ito T, Sakakibara R, Yasuda K, Yamamoto T, Uchiyama T, Liu Z, Yamanishi T, Awa Y, Yamamoto K, Hattori T (2006) Incomplete emptying and urinary retention in multiple-system atrophy: when does it occur and how do we manage it? Mov Disord 21(6):816–823
20. Kabay S, Canbaz Kabay S, Cetiner M, Mestan E, Sevim M, Ayas S, Ozden H, Ozisik Karaman H (2016) The clinical and urodynamic results of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease. Urology 87:76–81
21. Kay GG, Ebinger U (2008) Preserving cognitive function for patients with overactive bladder: evidence for a differential effect with darifenacin. Int J Clin Pract 62(11):1792–1800
22. Kiss G, Madersbacher H, Poewe W (1998) Cortical evoked potentials of the vesicourethral junction--a predictor for the outcome of intravesical electrostimulation in patients with sensory and motor detrusor dysfunction. World J Urol 16(5):308–312
23. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, Carson C 3rd, Cheitlin M, Debusk R, Fonseca V, Ganz P, Goldstein I, Guay A, Hatzichristou D, Hollander JE, Hutter A, Katz S, Kloner RA, Mittleman M, Montorsi F, Montorsi P, Nehra A, Sadovsky R, Shabsigh R (2005) Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 96(12B):85M–93M
24. Leng WW, Blalock HJ, Fredriksson WH, English SF, McGuire EJ (1999) Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation. J Urol 161(3):758–763
25. Lew-Starowicz M, Gianotten WL (2015) Sexual dysfunction in patients with multiple sclerosis. Handb Clin Neurol 130:357–370
26. Linder J, Libelius R, Nordh E, Holmberg B, Stenlund H, Forsgren L (2012) Anal sphincter electromyography in patients with newly diagnosed idiopathic parkinsonism. Acta Neurol Scand 126(4):248–255
27. Lombardi G, Musco S, Kessler TM, Li Marzi V, Lanciotti M, Del Popolo G (2015) Management of sexual dysfunction due to central nervous system disorders: a systematic review. BJU Int 115(Suppl 6):47–56
28. Moore RA, Derry S, McQuay HJ (2005) Indirect comparison of interventions using published randomised trials: systematic review of PDE-5 inhibitors for erectile dysfunction. BMC Urol 5:18
29. Mostile G, Jankovic J (2009) Treatment of dysautonomia associated with Parkinson's disease. Parkinsonism Relat Disord 15(Suppl 3):S224–S232
30. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, Carson CC, Cunningham GR, Ganz P, Goldstein I, Guay AT, Hackett G, Kloner RA, Kostis J, Montorsi P, Ramsey M, Rosen R, Sadovsky R, Seftel AD, Shabsigh R, Vlachopoulos C, Wu FC (2012) The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 87(8):766–778

31. Peterson AC, Fraser M (eds) (2016) Urodynamics for the clinician. Springer, Wien/New York
32. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM (1999) Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 11(6):319–326
33. Sakakibara R, Matsuda S, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T (2003) The effect of intranasal desmopressin on nocturnal waking in urination in multiple system atrophy patients with nocturnal polyuria. Clin Auton Res 13(2):106–108
34. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M (2009) Sphincter EMG as a diagnostic tool in autonomic disorders. Clin Auton Res 19(1):20–31
35. Sakakibara R, Kishi M, Ogawa E, Tateno F, Uchiyama T, Yamamoto T, Yamanishi T (2011) Bladder, bowel, and sexual dysfunction in Parkinson's disease. Parkinsons Dis 2011:924605
36. Sakakibara R, Panicker J, Finazzi-Agro E, Iacovelli V, Bruschini H, Parkinson's Disease Subcomittee, The Neurourology Promotion Committee in The International Continence Society (2016) A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn 35:551–563
37. Sato S, Hatanaka T, Yuyama H, Ukai M, Noguchi Y, Ohtake A, Taguchi K, Sasamata M, Miyata K (2012) Tamsulosin potently and selectively antagonizes human recombinant α(1A/1D)-adrenoceptors: slow dissociation from the α(1A)-adrenoceptor may account for selectivity for α(1A)-adrenoceptor over α(1B)-adrenoceptor subtype. Biol Pharm Bull 35(1):72–77
38. Schurch B, de Sèze M, Denys P, Chartier-Kastler E, Haab F, Everaert K, Plante P, Perrouin-Verbe B, Kumar C, Fraczek S, Brin MF (2005) Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. Botox Detrusor Hyperreflexia Study Team. J Urol 174(1): 196–200
39. Segraves RT (2003) Emerging therapies for female sexual dysfunction. Expert Opin Emerg Drugs 8(2):515–522
40. Shannon J, Jordan J, Costa F, Robertson RM, Biaggioni I (1997) The hypertension of autonomic failure and its treatment. Hypertension 30(5):1062–1067
41. Stohrer M, Castro-Diaz D, Chartier-Kastler E, Kramer G, Mattiasson A, Wyndaele JJ (2007) Guidelines on neurogenic lower urinary tract dysfunction. Prog Urol 17(3):703–755
42. Tison F, Arne P, Sourgen C, Chrysostome V, Yeklef F (2000) The value of external anal sphincter electromyography for the diagnosis of multiple system atrophy. Mov Disord 15(6): 1148–1157
43. Todorova A, Vonderheid-Guth B, Dimpfel W (2001) Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol 41(6):636–644
44. Virseda-Chamorro M, Salinas-Casado J, Lopez-Garcia-Moreno AM, Cobo-Cuenca AI, Esteban-Fuertes M (2013) Sexual dysfunction in men with spinal cord injury: a case-control study. Int J Impot Res 25(4):133–137. doi:10.1038/ijir.2013.1. Epub 2013 Feb 21
45. Vodusek DB (2005) How to diagnose MSA early: the role of sphincter EMG. J Neural Transm 112(12):1657–1668
46. Wallace SA, Roe B, Williams K, Palmer M (2004) Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev (1):CD001308
47. Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP (1994) Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain 117(Pt 4):835–845
48. Winge K, Fowler CJ (2006) Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. Mov Disord 21(6):737–745

Gastrointestinal Dysfunction

6

Roberta Granata, Eschlböck Sabine, Herbert Tilg, and Gregor Wenning

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The present chapter is divided into three sections. In the first part, the diagnostic work-up of gastrointestinal (GI) dysfunction is discussed. The second focuses on specific disorders that involve gastrointestinal autonomic system followed by the last section, which provides an overview of specific management.

R. Granata • E. Sabine • G. Wenning (✉)
Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria
e-mail: roberta.granata@i-med.ac.at; gregor.wenning@i-med.ac.at

H. Tilg
Department of Gastroenterology, Medical University of Innsbruck, Innsbruck, Austria

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6.1 Diagnostic Work-Up

6.1.1 Gastrointestinal Dysfunction

Gastrointestinal autonomic dysfunction may result from primary dysautonomias (e.g. pure autonomic failure (PAF), multiple system atrophy (MSA)), but a more common scenario is a systemic disorder (e.g. diabetes mellitus) resulting in autonomic dysfunction [3] (see Fig. 6.1). Gastrointestinal autonomic dysfunction is mostly non-specific and manifests with a combination of various symptoms and different degrees of severity. The entire gastrointestinal tract can be affected leading to a plethora of features. Symptoms of the proximal GI tract include for example dysphagia, nausea or epigastric pain and involvement of distal GI tract results in obstipation, diarrhoea and faecal incontinence (see Fig. 6.2). Diagnosis and

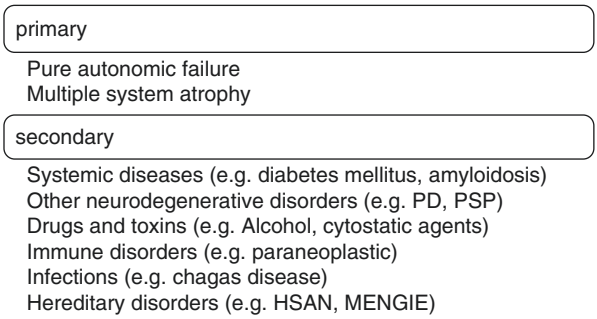

Fig. 6.1 Aetiology of gastrointestinal autonomic dysfunction (Modified from Bittinger et al. [3] with permission from Springer Science and Media)

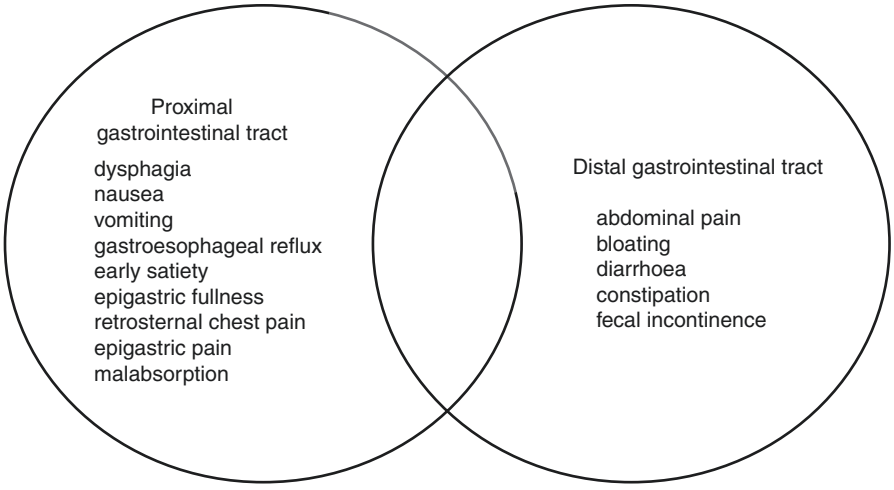

Fig. 6.2 Gastrointestinal manifestations arising from autonomic dysfunction [12]

treatment of gastrointestinal autonomic disorders are still challenging in clinical practice and require a detailed assessment and specific management.

For pathophysiology see Sect. 1.2.3.

6.1.2 History Taking and Red Flags

Gastrointestinal autonomic dysfunction includes a variety of unspecific symptoms. Accurate history taking and identification of red flags are pivotal for diagnosis. Detailed assessment of gastrointestinal complaints encompasses symptom onset, chronology as well as frequency, character and location of current GI symptoms. Frequency of defaecation as well as stool colour and consistency and events of haematochezia or melaena are essential for diagnosis. Patients should be asked about dietary habits and aggravating and alleviating factors of symptoms. Further evaluation includes comorbidities, past surgical history, current treatment as well as family and social history. Red flags that may suggest gastrointestinal autonomic dysfunction are summarised in Fig. 6.3 – See also Sect. 2.2.4.1 for reference.

6.1.3 Physical Examination

Based on historical features, general physical examination needs to be performed. In the first step, physical examination should focus on signs of gastrointestinal diseases (ascites, gynaecomastia, abdominal bruits, hernial orifices, alterations of the

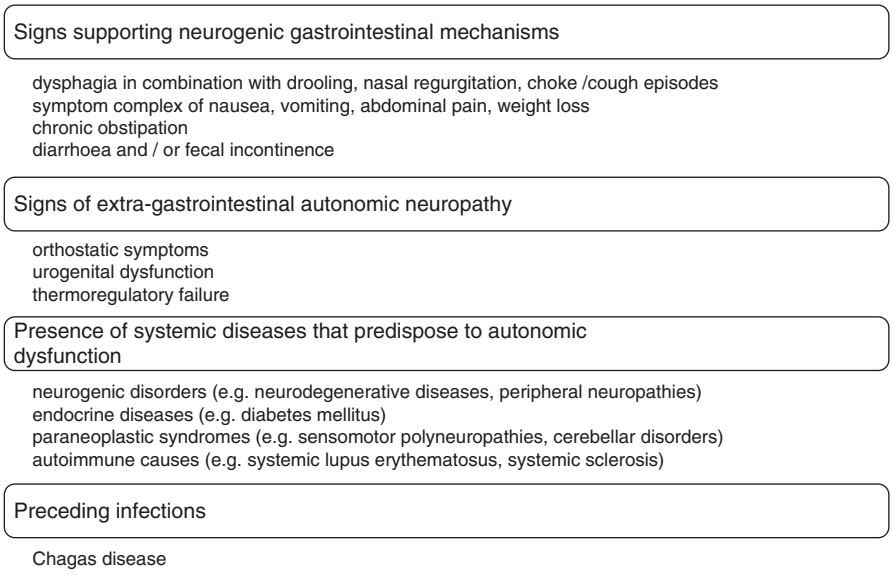

Fig. 6.3 Red flags suggesting gastrointestinal autonomic involvement [3, 44]

skin, eyes and hands), which are important for differential diagnosis, and further encompasses abdominal auscultation, percussion and palpitation. Digital rectal examination should be conducted to complete physical examination.

6.1.4 Laboratory Tests

According to the predominating symptoms and differential diagnosis, the following laboratory tests should be considered: full blood count, C-reactive protein, erythrocyte sedimentation rate, thyroid function tests, liver function tests, amylase, creatinine, urea, electrolytes, calcium, glucose, vitamin B12, electrophoresis, plasma autoantibodies and urinalysis [26, 31]. Special laboratory tests may be necessary in selected cases.

Autonomic Neuropathies Antibodies (anti-Hu, anti-nicotinic acetylcholine receptor antibodies, anti-Ri, cytoplasmic antigens (amphiphysin, anti-Yo), voltage-gated neuronal potassium channel complex (VGKC), calcium channel antibodies, glutamic acid decarboxylase 65 (GAD65), peripherin-IgG) are detected in serum or cerebrospinal fluid. Specific genetic tests may be considered for the diagnosis of inherited neuropathies [31]. For diagnostic work-up of autoimmune autonomic ganglionopathy, antiganglionic nicotinic acetylcholine receptor (AChR) (α3 subunit) antibodies may provide additional information [48]. Nonetheless, seronegativity has been reported in about 50% of cases with clinical features of subacute onset of multidomain autonomic failure suggesting an immune-mediated autonomic ganglionopathy [36].

Chagas Disease In acute phase, organisms may be detected in Giemsa-stained smears from tissue or cultivated in special media. Chronic phase serology or molecular biological tests may be helpful for diagnosis [4].

6.1.5 Investigations

Diagnostic work-up is difficult, because no specific assessment for GI autonomic neuropathy is available and limited to the detection of its sequela [3]. Nevertheless, detailed evaluation (see Fig. 6.4) is mandatory to define aetiology and fundamental for tailored therapy.

Dysphagia is a common symptom and may occur due to mechanical block or dysmotility. Difficulties in swallowing associated with drooling, nasal regurgitation, choke and cough episodes suggest neurogenic mechanisms [8], which result from sensorimotor impairment and can affect oral, pharyngeal or oesophageal phase of swallowing [44]. Although upper GI endoscopy including endoscopic biopsy per se does not diagnose motility disorders, endoscopy should be considered if structural abnormalities are suspected. Further investigations include videofluoroscopy to assess oropharyngeal dysfunction [33] and radiological investigation with barium swallow for detection of oesophageal dysmotility and structural abnormalities. In

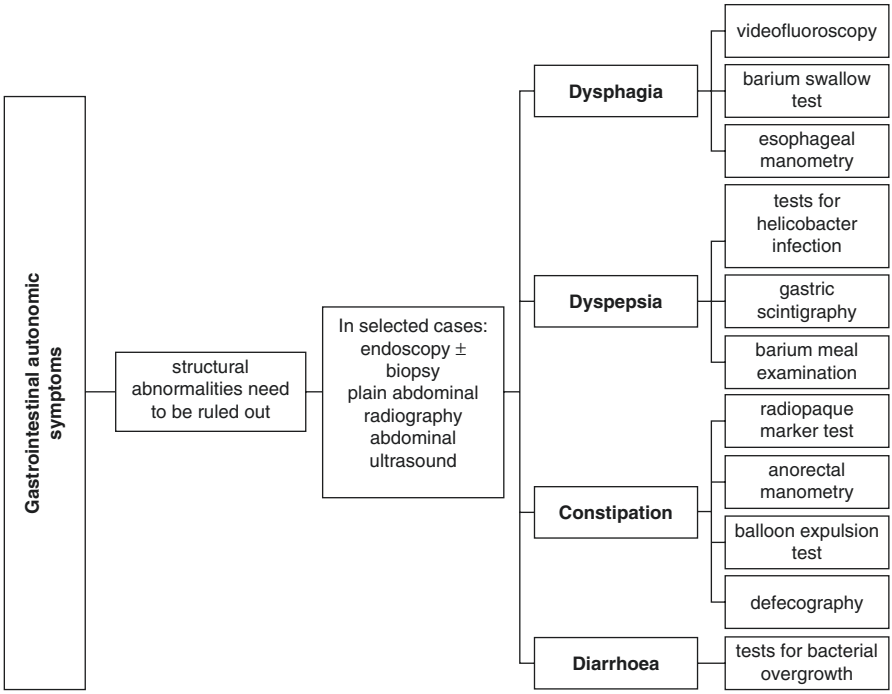

Fig. 6.4 Investigations of gastrointestinal symptoms (Modified from Fasano et al. [14] with permission from Elsevier)

case of normal barium swallow test and unexplained dysphagia or suspicion of oesophageal motility disorder, oesophagus manometry is of particular value [4].

Upper GI endoscopy is the predominant diagnostic modality to evaluate dyspepsia, and non-invasive tests including urea breath test, stool antigen test and serology are available to detect helicobacter infection [14]. Gastroparesis and delayed gastric emptying need to be evaluated by gastric scintigraphy, which is performed with radiolabelled digestible solids or liquids [10]. Although barium meal examination may be performed to detect gastric dysmotility, gastric scintigraphy remains the gold standard [4].

Assessment of chronic constipation resulting from neurologic disorders requires specific examination. In the first step, anorectal diseases, intestinal obstruction, metabolic/endocrine causes and drugs need to be ruled out. Therefore, to exclude structural diseases, patients younger than 50 years and without alarm signs (e.g. fever, weight loss, blood in the stools) should undergo sigmoidoscopy. In patients older than 50 years, colonoscopy or sigmoidoscopy in combination with barium enema examination is recommended [28]. For the assessment of colonic transit time, radiopaque marker test is considered as the standard measurement. In patients, which have clinical features that suggest a defecatory disorder, physiological testing is further recommended and includes anorectal manometry and balloon expulsion test. Defecography may be necessary to definitively exclude structural abnormalities in the rectum [26].

The pathomechanisms of diarrhoea are multifactorial. Common causes comprise infections (viral, bacterial, parasites, protozoa), inflammatory diseases (Crohn's disease, ulcerative colitis), colorectal cancer, coeliac disease and drug-induced diarrhoea, which need to be ruled out in the first step. Colonoscopy in combination with biopsy may be performed to definitely exclude malignancy and colitis. In the setting of gastrointestinal autonomic dysfunction, increased bacterial colonisation of the small intestine may lead to diarrhoea and malabsorption of nutrients [4] and can be established by breath hydrogen testing and jejunal aspirate [17].

6.2 Autonomic Dysfunction and the Gastrointestinal Nervous System

6.2.1 Gastrointestinal Autonomic Dysfunction in Neurodegenerative Diseases

In the last years, an increasing similarity of pathological mechanisms involving both the central and the peripheral gastrointestinal nervous system has been recognised in most neurodegenerative diseases. Intra- and extracellular inclusions of misfolded proteins are present in numerous CNS structures and sympathetic and spinal ganglia, as well as in the gastrointestinal plexus, with a different pattern and density of distribution in various neurodegenerative diseases. Like prion disorders, these protein aggregates can migrate from periphery (myenteric, submucosal plexus via autonomic innervation) to spinal cord, brainstem and other CNS structures or vice versa [13]. Some authors postulate the gastrointestinal tract as the origin of some neurodegenerative diseases, such as Parkinson's disease or MSA, dysfunction of the GI tract being a common premotor sign in these conditions [5, 7, 37, 49].

α-Synuclein aggregates forming Lewy bodies and Lewy neurites represent the pathological hallmark of Parkinson's disease and dementia with Lewy bodies and are found in early phases of the disease (according to Braak PD pathology stages) [6] in the dorsal vagal nucleus, olfactory bulb, midbrain and neostriatum. Lewy bodies are also widely present in the spinal cord, sympathetic ganglia, parasympathetic nervous system and enteric nervous system accounting for common gastrointestinal premotor symptoms such as slowing of gastrointestinal motility inducing dyspepsia, oesophageal achalasia and constipation [7, 38]. The presence of Lewy bodies in the submandibular gland and the related sympathetic and parasympathetic structures might explain the reduced salivary secretion in early stages of PD. Constipation is much more frequent in PD patients than in the healthy population [22], and people suffering of constipation have a 3.3- to 4.2-fold risk of developing PD [29]. Almost 90% of PD patients suffer of constipation, frequently worsening with disease progression [14]. Reduced gastric emptying is also present, causing upper gastrointestinal symptoms, but also interfering with optimal absorption of levodopa and consequently with optimal therapy efficacy and worsening levodopa long-term side effects such as fluctuations [32].

Dopaminergic medications can also produce gastrointestinal side effects, such as reduced gastrointestinal motility, whereas subthalamic nucleus-deep brain stimulation (STN-DBS) has been reported to improve gastrointestinal PD symptoms, such as delayed gastric emptying [32].

In MSA filamentous α-synuclein glial cytoplasmic inclusions (GCIs) are widely distributed. Massive autonomic dysfunction characterises these neurodegenerative diseases such as MSA and PAF including dysphagia and anal incontinence.

Gastrointestinal dysfunction may also be present in patients with AD and related tauopathies such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). These features likely reflect deposition of tau-positive neurofibrillary tangles (NFTs) in autonomic areas of the brain and spinal cord. Comorbid Lewy body pathology may also contribute to gastrointestinal dysfunction in Alzheimer's disease (AD). No NFTs have been reported in the myenteric plexus.

6.2.2 Gastrointestinal Autonomic Dysfunction in Peripheral Autonomic Neuropathies

Sympathetic and parasympathetic autonomic nerves (ANS) are constituted of small myelinated and unmyelinated fibres, the latter being predominant (about 80%). Most metabolic, hereditary, autoimmune, paraneoplastic and toxic neuropathies involve autonomic nerve fibres and may cause gastrointestinal autonomic dysfunction.

Among the metabolic neuropathies, the diabetic neuropathy is the most common. Hyperglycaemia increases apoptosis-activating ATP-sensitive K+-channels leading to loss of enteric neurons within myenteric and submucosal plexus, sympathetic ganglia and vagus nucleus, as well as of interstitial cells of Cajal (ICC). Other pathogenetic mechanisms of neuronal damage in diabetes mellitus (DM) involve decreased neuronal growth factor, increased circulating free fatty acids, altered transforming growth factor beta and decreased antioxidants such as glutathione [50]. Also reduced blood circulation and autoimmune/inflammatory response may play a role in neural damage.

Denervation mainly involves sympathetic nerve terminals, which have the function of reducing gut motility, and parasympathetic excitatory nerves being at least at the beginning spared from damage. Loss of ICC is associated with impaired relaxation of gastric fundus and the absence of slow-phase peristaltic movements. Delayed gastric emptying and increased distal retention lead to gastroesophageal reflux, early satiety sensation, gastric pain and vomiting [23, 39, 50]. Symptomatic gastroparesis is a rare complication of diabetic neuropathy accounting for 4.8% in type 1 diabetes and 1% in type 2 diabetes. The decrease of NO release from vagal efferent fibres and of the enzyme responsible for its generation, nNOS, has been postulated to play an important role in pathogenesis of delayed gastric emptying [21].

Reduced gut movements produce bacterial overgrowth and diarrhoea, which, together with faecal incontinence, is a common symptom of diabetic neuropathy.

Other mechanisms potentially accounting for diarrhoea include the presence of accelerated intestinal transit as suggested by some animal models [50].

Hereditary sensory and autonomic neuropathies (HSAN) represent a group of rare disorders characterised by degeneration of peripheral sensory and autonomic neurons leading to variable sensory and autonomic symptoms. HSAN type 3 is the disorder which shows most autonomic symptoms. HSAN 3, also known as Riley-Day syndrome or familiar dysautonomia, is a rare autosomic recessive disorder affecting principally Ashkenazi Jews. It is due to a mutation on chromosome 9q leading to depletion of IKAP/EPL1 protein which affects cell motility [45]. This genetic mutation results in a marked depletion of small C-fibres in the sensory and autonomic nervous system which can be demonstrated in the skin and on peripheral blood vessels. Children develop early and severe symptoms such as sensory loss (with frequent trauma and self-mutilation as consequence), the absence of tears, swallowing difficulties, pneumonia, orthostatic blood pressure dysregulation, autonomic crises with vomiting and gastrointestinal dysmotility. Oropharyngeal problems occur early in children with HSAN 3 which present with poor sucking, swallowing difficulties and consequent drooling. Vomiting can occur daily in response to physical or emotional stress [42].

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease caused by mutations of the gene encoding thymidine phosphorylase. External ophthalmoplegia, gastrointestinal motility disorders, peripheral neuropathy and leukoencephalopathy are the main characteristics of this disease. Patients are often cachectic and suffer neuropathic pain [41].

Idiopathic, postinfectious or paraneoplastic autoimmune neuropathies can cause acute or subacute autonomic failures, including severe gastrointestinal dysmotility or pseudo-obstruction. Symptoms, such as vomiting, abdominal pain and constipation, are similar to those occurring due to mechanical obstruction. Oesophageal dysmotility (including achalasia) may also be present. Gastrointestinal hypermotility may occur in autoimmune dysautonomias. The term autoimmune gastrointestinal dysmotility (AGID) is generally accepted to indicate gastrointestinal manifestations of autoimmune autonomic neuropathies. In paraneoplastic disorders, dysautonomia can occur as isolated disorder or in combination with other neurological findings, such as sensorimotor polyneuropathies, cerebellar disorders and limbic encephalitis.

6.2.3 Gastrointestinal Autonomic Dysfunction in Infections: Chagas Disease

Autonomic dysfunction of gastrointestinal tract can occur in case of a parasite infection, the so-called American trypanosomiasis or Chagas disease, which is caused by the flagellate protozoan *Trypanosoma cruzi* [43]. The chronic form has a variable

course, 60% of individuals are asymptomatic and 20–40% of affected people present cardiomyopathy or gastrointestinal dysautonomia.

6.3 Therapy of Gastrointestinal Autonomic Dysfunction

Non-pharmacological treatment of gastrointestinal dysmotility includes dietary measures. Patients should avoid excessive food intake and instead eat small frequent meals, chew their food well and avoid fibre and fats. The judicious use of some drugs which affects gastrointestinal motility such as anticholinergics and opiates is also recommended.

In general, symptomatic therapies of gastrointestinal autonomic dysfunction include antidopaminergic agents, cholinesterase inhibitors and drugs which improve gastrointestinal motility, such as erythromycin or serotoninergic agents (i.e. the selective 5-HT4 receptor agonists prucalopride or mosapride), antiemetics and laxatives. Simple analgetics may be useful in the treatment of abdominal pain (*see* Table 6.1).

Table 6.1 Symptomatic treatment of gastrointestinal autonomic symptoms

	Drug	Doses	Action	Side effects
Prokinetics	Metoclopramide	10 mg/3×	Antidopaminergic (central and peripheral)	Drowsiness, fatigue, extrapyramidal effects
	Itopride	50 mg/3×	Antidopaminergic (peripheral), acetylcholinesterase inhibitor	Abdominal pain and diarrhoea
	Domperidone	10 mg/3×	Antidopaminergic (peripheral)	Dizziness, dry mouth, nervousness
	Prucalopride	2–4 mg/1×	Selective 5-HT4 receptor agonists	Headache, nausea, abdominal cramps and diarrhoea
	Lubiprostone	24 mg/2×	Activates type-2 chloride channels	Nausea, diarrhoea, abdominal pain
	Linaclotide	195/290 mcg/×1	Activates guanylate cyclase C	Diarrhoea
	Macrolide antibiotics (erythromycin)	250–500-mg/×2	Motilin agonists	Antimicrobial effect

(continued)

Table 6.1 (continued)

	Drug	Doses	Action	Side effects
Antiemetics	Prochlorperazine	5–10 mg	Antidopaminergic, anticholinergic (central)	Extrapyramidal effects
	Ondansetron and granisetron	8 mg	5-HT3 antagonists	Diarrhoea or constipation, headache, drowsiness, fatigue
	THC (tetrahydrocannabinol)	5–10 mg/×2–3	CB1 and CB2 receptor agonist in the CNS	Unsteadiness, dizziness, drowsiness, confusion
	Diphenhydramine	50 mg/×1–3	H1 receptor agonists, antimuscarinic	Sedation, drowsiness, increased heart rate, urinary retention
Analgetics	Gabapentin	300–800 mg/×3	GABA receptor agonist	Dizziness, fatigue
	Pregabalin	75–150 mg/×2–3	GABA analogue	Dizziness, fatigue
	Oxycodone	10–40 mg/day	μ-Opioid receptor antagonist	OIBD, dependence, addiction
	Naloxone	10–40 mg/day	μ-Opioid receptor antagonists	OIBD, dependence, addiction
	Tricyclic antidepressants	Dose depends on formulation	Serotonin-norepinephrine reuptake inhibitors	Dry mouth, urinary retention, constipation, cognitive impairment
Laxatives	Saccharin, lactulose, sorbitol macrogol, polyethylene glycol 3350, magnesium hydroxide, sodium biphosphate	Dose depends on formulation	Osmotic activity	Abdominal distention and pain, diarrhoea, dehydration

The dopamine receptor antagonist metoclopramide is used in case of gastroparesis [1]. It has both a peripheral (in the upper gastrointestinal tract) and a central effect. Being an inhibitor of CYP2D6, enzyme 45 should not be used in combination with antidepressants such as tricyclics, selective serotonin reuptake inhibitors and antidepressants acting as serotonin-noradrenalin reuptake inhibitors

(venlafaxine or duloxetine), which could increase the risk of extrapyramidal side effects. Drowsiness and fatigue represent the most common side effects of metoclopramide. Due to possible extrapyramidal effects, it should be avoided as a long-term treatment in patients with extrapyramidal diseases and in younger patients and children [27].

Itopride is a peripheral antidopaminergic drug that also increases acetylcholine levels due to acetylcholinesterase inhibition and can be used as prokinetic agent. It is metabolised through a mono-oxidase system, and it can be used relatively safely with other drugs such as antidepressants. Due to its exclusive peripheral antidopaminergic effects, itopride can be used also in patients with extrapyramidal diseases (i.e. PD) [27].

Domperidone, a dopaminergic receptor D-2 antagonist which does not cross the blood-brain barrier, is very useful to accelerate gastric emptying and represents the first-choice treatment for delayed gastric emptying, nausea and vomiting in PD or MSA patients [40].

The use of macrolide antibiotics may be considered in improving gastrointestinal dysmotility accelerating, such as motilin agonists, the MMC (migrating motor complex). Their chronic use is however limited due to the contemporary antimicrobial effect [25, 32].

Prucalopride and mosapride such as selective 5-HT4 receptor agonists; lubiprostone, which activates type-2 chloride channels; and linaclotide which activates guanylate cyclase C represent newer prokinetic drugs [9, 27].

Some prokinetic agents, such as the gastric-derived hormone ghrelin, ghrelin agonists and motilin, represent interesting treatment options for reduced gastric motility in diabetic neuropathies and PD. Some of these drugs are available only for study purposes, and controlled studies are needed to further evaluate the safety and efficacy of these medications [34, 46].

Linaclotide is a prokinetic drug that modulates chloride secretion of the intestinal epithelial cells through activation of guanylate cyclase C. Linaclotide improves defaecation by stimulating GI secretion and motility, increasing stool frequency as well as stool weight. The main adverse event of linaclotide is diarrhoea [35]. Linaclotide can be used for chronic constipation and may be useful also in case of opioid-induced bowel dysfunction (OIBD) [9, 27].

Phenothiazines such as prochlorperazine are potent neuroleptics and commonly utilised as therapy for nausea and vomiting. The antiemetic effect is due to the central action on dopaminergic and cholinergic receptors; however, their use is limited due to a potential risk of extrapyramidal side effects. Other antiemetic drugs include the 5-HT3 antagonists ondansetron and granisetron, cannabinoids, opioid agonists, benzodiazepines and H1 receptor agonists, such as diphenhydramine.

Laxatives can be used in patients with chronic constipation although their side effects such as dehydration and intestinal occlusion have to be considered [18, 24]. The most commonly used group of laxatives comprises osmotic agents such as lactulose, sorbitol, macrogol, polyethylene glycol 3350, magnesium and sodium salts

or detergents that increase GI secretion and decrease surface tension, such as docusate and stimulants like sennosides and bisacodyl that promote gastrointestinal motility [27].

In case of chronic abdominal pain, antineuralgic therapy with gabapentin and pregabalin, also in combination with tricyclic and tetracyclic antidepressants, may be helpful. Other analgetic drugs including weak opiates, such as naloxone and oxycodone, should be used very sparsely and only in refractory cases due to their gastrointestinal side effects such as opioid-induced bowel dysfunction (OIBD) and physical dependence and addiction [27].

In severe cases of pseudo-obstruction and ileus, surgical procedures may be necessary. Gastric electric stimulation is an effective treatment in severe cases of gastroparesis and drug-refractory vomiting [20].

Intrapyloric injection of botulinum toxin injection in some case of pylorospasm has been reported as efficacious in some open-label studies. Controlled trials have not confirmed this improvement [16, 19].

AGID (autoimmune gastrointestinal dysmotility) due to postinfectious dysautonomia is usually self-limited and requires symptomatic treatment only in the acute phase. Other forms of AGID (i.e. paraneoplastic or as manifestation of an idiopathic autoimmune disorder) may require immunotherapy with intravenous immune globulin (IVIG) or methylprednisolone (IVMP), especially if neural-specific immunoglobulins are detected in serum, although data regarding efficacy of this therapy are controversial. In case of a good response, long-term maintenance immunotherapy can be considered [15].

Two nitro-heterocyclic drugs currently represent the only treatment options for Chagas disease: benznidazole and nifurtimox. However, these drugs provide a lot of side effects, such as intolerance, allergic reactions and fever, being often very challenging to treat patients properly. Other effective drugs are currently needed, and at the present, a few drug trials are ongoing [11].

In patients suffering of synucleinopathies (PD, MSA), domperidone and selective 5-HT4 receptor agonists (i.e. prucalopride, mosapride) represent useful drugs to accelerate gastrointestinal motility especially in case of gastroparesis augmented by L-dopa fluctuations [30, 47]. Improved gastric emptying increases L-dopa absorption and induces an improvement of motor symptoms. Interesting data of improved gastrointestinal motility have been reported after subthalamic nucleus-deep brain stimulation (STN-DBS) which represent an effective therapy option in selected PD patients. STN-DBS may improve autonomic gastrointestinal dysmotility directly due to the connections of STN and autonomic centres or indirectly due to the reduction of dopaminergic therapy after STN-DBS [2]. Further treatment options in PD patients may be considered and include liquid levodopa formulations and parenteral routes (e.g. rotigotine transdermal patch, subcutaneous apomorphine, intrajejunal levodopa infusion) [14].

Case Report 1

A 64-year-old male patient with a history of Parkinson's disease and disease duration of 10 years complains about dysphagia and dyspepsia.

At neurological examination, a left-sided Parkinsonian syndrome with bradykinesia, rigidity and classic pill-rolling tremor is present. Furthermore, gait disturbances and bilaterally reduced arm swing are present. The patient reports no further signs of autonomic dysfunction. Although the patient usually has a good levodopa response, he suffers from disabling motor fluctuations.

Examinations to evaluate upper gastrointestinal symptoms include videofluoroscopy, which excludes oropharyngeal pathology. For the assessment of oesophageal motility, barium swallow exam is performed and demonstrates oesophageal dysmotility. Upper GI endoscopy, which is performed to rule out ulcers and malignancy, shows food residue in a fasted stomach suggesting gastric stasis. Therefore, gastric scintigraphy is conducted and confirms delayed gastric emptying.

Because of impairment of oesophageal and gastric motility, which leads to reduced absorption of levodopa and worsening of levodopa long-term side effects, subcutaneous apomorphine is recommended and provides improvement of motor symptoms.

Case Report 2

A 30-year-old woman is examined because of abdominal pain, weight loss, intractable obstipation and vomiting. The patient is cachectic and physically weakened because food ingestion is nearly impossible.

Medical history taking reveals gastrointestinal symptoms for 10 years. Additionally, the patient suffers from multidomain autonomic failure including urinary retention, recurrent syncope, hypohidrosis, sicca syndrome and Raynaud's phenomenon. Extensive examinations including autonomic function testing and immunological laboratory have been conducted and have ruled out other immunological disorders.

Broad examination of proximal and distal gastrointestinal tract confirms gastroparesis and severe colonic motility dysfunction but shows normal duodeno-cecal transit time. In the course of the disease, the patient is reliant on parenteral nutrition, and after double-barrel colostomy, she undergoes subtotal colectomy because of persistent gastrointestinal dysfunction. Histopathological examination reveals segmental hypogangliosis and

T-lymphocytic ganglionitis. The patient is given immunosuppressive therapy, which immediately leads to improvement of gastrointestinal symptoms. Autoimmune autonomic ganglionopathy (AAG) is suspected, but screening for antibodies to the ganglionic nicotinic acetylcholine receptor is negative.

Despite negative ganglionic nicotinic acetylcholine antibodies, which are found in only 50% of patients with AAG, clinical presentation and response to immunosuppressive therapy indicate the presence of AAG. The patient receives steroid therapy and tacrolimus stabilising the clinical disease course.

References

1. Abell TL, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, McCallum RW, Olden KW, Parkman HP, Parrish CR, Pasricha PJ, Prather CM, Soffer EE, Twillman R, Vinik AI (2006) Treatment of gastroparesis: a multidisciplinary clinical review. Neurogastroenterol Motil 18(4):263–283
2. Arai E, Arai M, Uchiyama T, Higuchi Y, Aoyagi K, Yamanaka Y, Yamamoto T, Nagano O, Shiina A, Maruoka D, Matsumura T, Nakagawa T, Katsuno T, Imazeki F, Saeki N, Kuwabara S, Yokosuka O (2012) Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. Brain 135:1478–1485
3. Bittinger M, Barnert J, Wienbeck M (1999) Autonomic dysfunction and the gastrointestinal tract. Clin Auton Res 9(2):75–81
4. Boulton R, Cousins C, Gupta S, Hodgson H (2011) Gastroenterology, 2nd edn. London: Manson Publishing. ISBN: 978–1–84076-068-2
5. Braak H, de Vos RA, Bohl J, Del Tredici K (2006) Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. Neurosci Lett 396:67–72
6. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211
7. Braak H, Sastre M, Bohl JR, de Vos RA, Del Tredici K (2007) Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. Acta Neuropathol 113:421–429
8. Buchholz DW (1994) Dysphagia associated with neurological disorders. Acta Otorhinolaryngol Belg 48(2):143–155
9. Busby RW, Kessler MM, Bartolini WP, Bryant AP, Hannig G, Higgins CS, Solinga RM, Tobin JV, Wakefield JD, Kurtz CB, Currie MG (2013) Pharmacologic properties, metabolism, and disposition of linaclotide, a novel therapeutic peptide approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. J Pharmacol Exp Ther 344(1):196–206
10. Camilleri M, Shin A (2013) Novel and validated approaches for gastric emptying scintigraphy in patients with suspected gastroparesis. Dig Dis Sci 58(7):1813–1815
11. Chatelain E (2015) Chagas disease drug discovery: toward a new era. J Biomol Screen 20(1):22–35
12. Chelimsky G, Chelimsky TC (2003) Evaluation and treatment of autonomic disorders of the gastrointestinal tract. Semin Neurol 23(4):453–458
13. Cushman M, Johnson BS, King OD, Gitler AD, Shorter J (2010) Prion –like disorders: blurring the divide between transmissibility and infectivity. J Cell Sci 123:1191–1201
14. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF (2015) Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 14(6):625–639

15. Flanagan EP, Saito YA, Lennon VA, McKeon A, Fealey RD, Szarka LA, Murray JA, Foxx-Orenstein AE, Fox JC, Pittock SJ (2014) Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. Neurogastroenterol Motil 26(9):1285–1297
16. Friedenberg FK, Parkman HP (2006) Delayed gastric emptying: whom to test, how to test, and what to do. Curr Treat Options Gastroenterol 9(4):295–304
17. Grace E, Shaw C, Whelan K, Andreyev HJ (2013) Review article: small intestinal bacterial overgrowth – prevalence, clinical features, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther 38(7):674–688
18. Holzer P, Ahmedzai SH, Niederle N, Leyendecker P, Hopp M, Bosse B, Spohr I, Reimer K (2009) Opioid-induced bowel dysfunction in cancer-related pain: causes, consequences, and a novel approach for its management. J Opioid Manag 5(3):145–195
19. Hoogerwerf WA, Pasricha PJ (1999) Botulinum toxin for spastic gastrointestinal disorders. Baillieres Best Pract Res Clin Gastroenterol 13(1):131–143
20. Jayanthi NV, Dexter SP, Sarela AI (2013) Gastric electrical stimulation for treatment of clinically severe gastroparesis. J Minim Access Surg 9(4):163–167
21. Kashyap P, Farrugia G (2011) Oxidative stress: key player in gastrointestinal complications of diabetes. Neurogastroenterol Motil 23:111–114
22. Kaye J, Gage H, Kimber A, Storey L, Trend P (2006) Excess burden of constipation in Parkinson's disease: a pilot study. Mov Disord 21(8):1270–1273
23. Kinekawa F, Kubo F, Matsuda K, Fujita Y, Tomita T, Uchida Y, Nishioka M (2001) Relationship between esophageal dysfunction and neuropathy in diabetic patients. Am J Gastroenterol Hepatol 96(7):2026–2032
24. Larkin PJ, Sykes NP, Centeno C, et al.; European Consensus Group on Constipation in Palliative Care (2008) The management of constipation in palliative care: clinical practice recommendations. Palliat Med 22(7):796–807
25. Larson JM, Tavakkoli A, Drane WE, Toskes PP, Moshiree B (2010) Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. Neurogastroenterol motil 16(4):407–413
26. Lembo A, Camilleri M (2003) Chronic constipation. N Engl J Med 349(14):1360–13608
27. Leppert W (2015) Emerging therapies for patients with symptoms of opioid-induced bowel dysfunction. Drug Des Devel Ther 9:2215–2231
28. Lieberman DA, Weiss DG (2001) One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 345(8):555–560
29. Lin C, Lin J, Liu Y, Chang C, Wu R (2014) Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. Parkinsonism Relat Disord 20:1371–1375
30. Liu Z, Sakakibara R, Odaka T, Uchiyama T, Uchiyama T, Yamamoto T, Ito T, Asahina M et al (2005) Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. Mov Disord 20:680–686
31. Longmore M, Wilkinson IB, Davidson EH, Foulkes A, Mafi AR (2012) Oxford Handbook of clinical medicine, 8th edn. Oxford University Press, Oxford
32. Marrinan S, Emmanuel AV, Burn DJ (2014) Delayed gastric emptying in Parkinson's disease. Mov Disord 29(1):23–32
33. Martin-Harris B, Jones B (2008) The Videofluorographic Swallowing Study. Phys Med Rehabil Clin N Am 19(4):769–785
34. McCallum RW, Lembo A, Esfandyari T, Bhandari BR, Ejskjaer N, Cosentino C, Helton N, Mondou E, Quinn J, Rousseau F, TZP-102 Phase 2b Study Group (2013) Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. Neurogastroenterol Motil 25(11):705–717
35. Müller-Lissner S (2013) Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments. Expert Opin Drug Metab Toxicol 9(4):391–401
36. Muppidi S, Vernino S (2013) Autoimmune autonomic failure. Hand Clin Neurol 117: 321–3277

37. Natale G, Pasquali L, Paparelli A, Fornai F (2011) Parallel manifestations of neuropathologies in the enteric and central nervous system. Neurogastroenterol Motil 23:1056–1065
38. Natale G, Pasquali L, Ruggieri S, Paparelli A, Fornai F (2008) Parkinson's disease and the gut: a well known clinical association in need of an effective cure and explanation. Neurogastroenterol motil 20:741–749
39. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Sato T, Haruna Y, Miyamoto T, Kanda T, Kawano S, Hori M (2004) Gastroesophageal reflux disease related to diabetes: Analysis of 241 cases with type 2 diabetes mellitus. J Gastroenterol Hepatol 19(3):258–265
40. Nishikawa N, Nagai M, Tsujii T, Iwaki H, Yabe H, Nomoto M (2012) Coadministration of domperidone increases plasma levodopa concentration in patients with Parkinson disease. Clin Neuropharmacol 35(4):182–184
41. Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimarães J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M (2000) Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol 47(6):792–800
42. Norcliffe-Kaufmann L, Kaufmann H (2012) Familial dysautonomia (Riley-Day syndrome): when baroreceptor feedback fails. Auton Neurosci 172:26–30
43. Pereira PCM, Navarro EC (2013) Challenges and perspectives of Chagas disease: a review. J Venom Anim Toxins Incl Trop Dis 19:1–34
44. Perkin GD, Murray-Lyon I (1998) Neurology and the gastrointestinal system. J Neurol Neurosurg Psychiatry 65(3):291–300
45. Slaugenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, Cuajungco MP, Liebert CB, Chadwick B, Idelson M, Reznik L, Robbins C, Makalowska I, Brownstein M, Krappmann D, Scheidereit C, Maayan C, Axelrod FB, Gusella JF (2001) Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet 68(3):598–605
46. Shin A, Wo JM (2015) Therapeutic applications of ghrelin agonists in the treatment of gastroparesis. Curr Gastroenterol Rep 17(2):430
47. Ueno N, Inui A, Satoh Y (2010) The effect of mosapride citrate on constipation in patients with diabetes. Diabetes Res Clin Pract 87:27–32
48. Vernino S, Sandroni P, Singer W, Low PA (2008) Invited article: autonomic ganglia: target and novel therapeutic tool. Neurology 70(20):1926–1932
49. Wakabayashi K, Mori F, Tanjo K, Orimo S, Takahashi H (2010) Involvement of the peripheral nervous system in synucleopathies, tauopathies and other degenerative proteinopathies of the brain. Acta Neuropathol 120:1–12
50. Yarandi SS, Srinivasan S (2014) Diabetic gastrointestinal motility disorders and the role of enteric nervous system: current status and future directions. Neurogastroenterol Motil 26(5):611–624

Autonomic Hyperactivity Syndromes

7

Walter Struhal and Heinz Lahrmann

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W. Struhal, Dr., PD (✉)
Chair, Department of Neurology, Karl Landsteiner University of Health Sciences, Site Tulln, Tulln, Austria
e-mail: walter.struhal@tulln.lknoe.at

H. Lahrmann
Private Office, Vienna 1030, Austria
e-mail: neurologe@lahrmann.at

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7.1 Case Introduction

In March, a 63-year-old accountant wanted to ride his motorbike from a shed, where he kept it in winter times, to his house to prepare it for the new season. Since this was only some 150 meters, he did not care to wear a helmet. After riding about half of the distance, he pulled the gas not noticing that the concrete at this very spot was covered with some gravel from winter times. His family heard a short revving of his engine, followed by crash noise, and immediately came to help. When paramedics arrived, he had Glasgow Coma Scale of 9, continuously worsening. Paramedics requested an air-bound emergency doctor transport to the hospital. Due to his diminishing consciousness, he was intubated before the helicopter left the site.

Emergency trauma room CT revealed a basal skull fracture, temporal right contrecoup hemorrhage, right subdural hematoma, and subarachnoidal hematoma (Fig. 7.1a). An intracranial transducer was placed; opening intracranial pressure

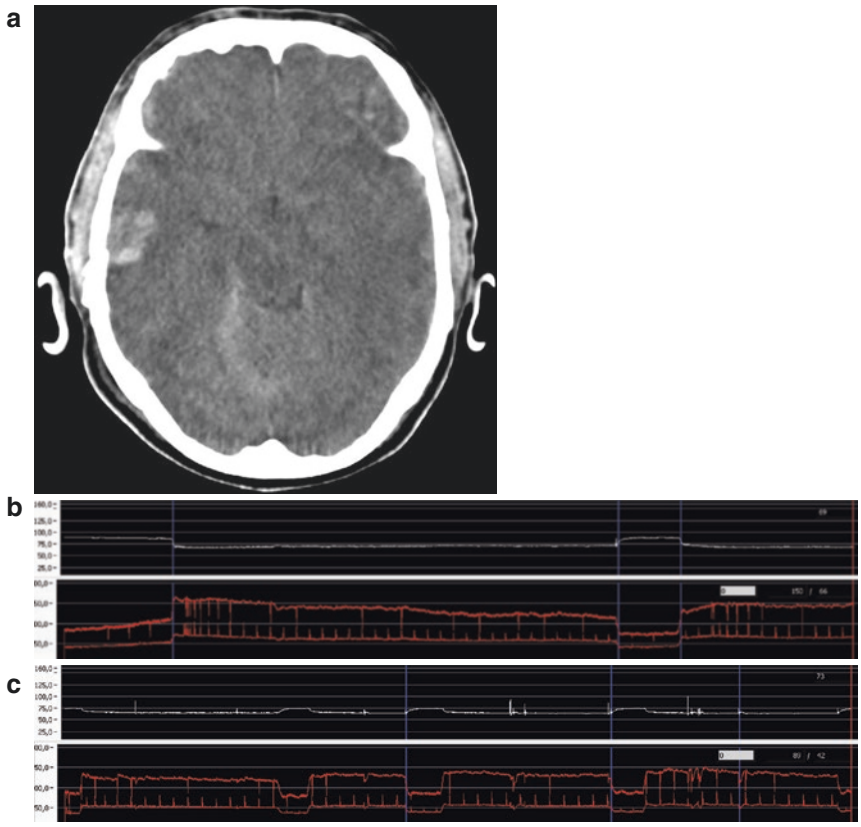

Fig. 7.1 (**a**) Admission CT scan showing temporal right contrecoup hemorrhage, right subdural hematoma, subarachnoidal hematoma, and basal skull fracture. (**b**) Autonomic monitoring day 1: fluctuations of heart rate, blood pressure according to intracranial pressure fluctuations. Upper trace (*white*) heart rate, lower trace (*red*) systolic and diastolic blood pressure. (**c**) Autonomic monitoring day 3: increased frequency of fluctuations. Upper trace (*white*) heart rate, lower trace (*red*) systolic and diastolic blood pressure

was 22 mmHg. Through intensive care management, the intracranial pressure could be controlled, but autonomic monitoring revealed severe fluctuations of heart rate and blood pressure, occurring at the very moment of intracranial pressure fluctuations (Fig. 7.1b). The frequency of fluctuations increased (Fig. 7.1c). On day 3, MRI revealed an additional left frontal coup hemorrhage. On day 5 the patient suffered cardiac arrest. Despite prolonged cardiopulmonary resuscitation at the intensive care ward, a sufficient circulation could not be restored, and the patient died.

7.1.1 Introduction

One of the most dangerous expressions of autonomic disease is autonomic hyperactivity, usually caused by a profound sympathetic increase.

Causes of autonomic hyperactivity include acute intracranial lesions (e.g., severe head trauma, hemorrhage, brain stem lesions) [1], spinal cord lesions causing autonomic dysreflexia, peripheral neuropathies (e.g., Guillain-Barré), drugs (intoxications), and alcohol withdrawal [2].

Features of autonomic hyperactivity
Fluctuations in
- Blood pressure
- Heart rate
- Respiratory function
- Body temperature

May include
- Agitation
- Sweating
- Flushing
- Piloerection
- Pupillary dilatation
- Muscle tone increase

Autonomic hyperactivity may mount in severe complications.

Parasympathetic increase, especially acute loss of modulation, might also cause severe or even life-threatening complications (hypotonia or bradycardia, paralytic ileus, or bladder dysfunction). They are much less common but occur in, e.g., patients suffering autonomic dysreflexia or generalized seizures.

Consequences of autonomic hyperactivities are baroreceptor reflex failure, heart rate fluctuations, ECG changes (see Fig. 7.1b, c), cardiac arrhythmias, blood pressure disturbances, chemoreceptor reflex failure, and respiratory complications in variable degrees. The most severe of these complications is the collapse of the cardiovascular function. Apart from measuring blood pressure, heart rate, and oxygenation, blood flow might be already evaluated at bedside (skin color, skin temperature). During intensive care monitoring, invasive circulation measurements are needed. Provocation factors should be avoided.

Provocative factors/triggers

- Pain including intestinal pain during bowel movement and body manipulation during nursing
- Tracheal suctioning
- Catheterization
- Bladder distention
- Pressure on the carotid sinus
- Eyeball pressure
- Loud and sudden noise

Autonomic hyperactivity needs urgent attention in identifying the lesion site and monitoring the patient.

7.2 Diagnosing Autonomic Involvement

In contrast to autonomic tests presented in Chaps. 2, 3, and 4, autonomic standard investigations are rarely accessible at an intensive care or critical care units. However, these patients are monitored, and several biosignals are of great help in hinting to autonomic disorders.

7.2.1 ECG [3]

The heart frequency is an important biomarker of autonomic dysfunction in intensive care patients. Tachycardia, bradycardia, or arrhythmia indicates sympathetic or parasympathetic overactivity (see Table 7.1). In addition, autonomic innervation of the heart leads to altered ECG morphologies. These include prolonged PQ and QT interval, T wave, and ST and U interval morphologies.

Table 7.1 Typical symptoms and causes of autonomic hyperactivity syndromes

Syndrome	Symptoms	Possible causes
Increased sympathetic drive	Hypertension, arrhythmia, ECG changes, hyperhidrosis	SAH, ICH, stroke
Sympathetic deafferenciation	Hypotension, orthostatic intolerance, bradycardia, anhidrosis	Acute lesion cervical spinal cord
Increased parasympathetic drive	Bradycardia, reflex asystole, hypersalivation, diarrhea	GBS, brain stem lesion, side effect of cholinergic drugs
Parasympathetic deafferenciation	Tachycardia, intestinal atonia, dry mouth, dry eyes	GBS, side effect of anticholinergic drugs
Complete autonomic deafferenciation	Hhypotonia, orthostatic intolerance, autonomic atonia	GBS, pandysautonomia, brain death
Changing vegetative states	Symptom oscillations from increased sympathetic to parasympathetic drive	GBS, tetanus
Intracranial pressure	Hypertension, bradycardia	ICH, cerebral edema, SDH

Adapted from Autonome Störungen et al. [3]

7.2.1.1 Blood Pressure

As discussed in Chaps. 1 and 3, the sympathetic nervous system regulates the arterial vessel constriction. Blood pressure is therefore a strong marker for sympathetic innervation in intensive care patients. This biomarker is best monitored "beat to beat" employing an arterial catheter. In patients with autonomic dysfunction, blood pressure trends might be valuable to monitor autonomic dysfunction.

7.2.1.2 General Management Considerations

Patients with autonomic hyperactivity should be managed at critical care wards including basic monitoring of ECG, temperature, respiratory frequency, continuous blood pressure, fluid balance (eventually invasive), and blood oxygenation.

As soon as the patient is initially stabilized, elaborate evaluation of the condition causing autonomic hyperactivity is necessary to initiate optimal treatment. Pursuing an approach as presented in Table 7.1 might prove valuable to derive an etiologic differential diagnosis.

Even if the condition is already well established at the onset of autonomic hyperactivity (e.g., head trauma, intracranial hemorrhage), reevaluation is mandatory, to exclude secondary complications such as hydrocephalus, drug effects, seizures, increasing brain edema, systemic inflammatory response syndrome (SIRS), or multiple organ dysfunction syndrome.

General management considerations include concise fluid management to maintain euvolemic conditions, exclusion or early treatment of infection, sufficient analgesia or analgosedation if necessary, and focused attention to triggering factors.

7.3 Syndromes

7.3.1 Sympathetic Hyperactivity

- Autonomic storm is considered in patients suffering extensive activation of the sympathetic nervous system. This activation might have three different pathophysiological mechanisms: sympathoadrenal discharge, Cushing's response, and end diencephalic "seizures."
- Typical signs of sympathoadrenal discharge are hypertension, tachycardia, increased cardiac output, and decreased vascular resistance. Autonomic hyperactivity is caused by increased sympathetic nerve activity due to severe CNS lesions, either with sympathetic neural discharge or excessive adrenal activity.
- Cushing's response on the contrary shows hypertension but bradycardia as well as slow irregular breathing. Causes are acute distortion of the lower brain stem or cerebral hematomas.
- Diencephalic "seizures" are characterized by acute hypertension, tachycardia, pupillary dilatation, and often extensive sweating. The pathophysiology is unclear; there is no convincing evidence for epileptic discharge. Causes might be closed head injuries resulting in a decorticate state or widespread axonal injury.

7.3.2 Specific Syndromes

7.3.2.1 Head Trauma

Paroxysmal sympathetic hyperactivity is a regular complication of head trauma patients. Disconnections involving the posterior corpus callosum and posterior limb of the internal capsule may play a role in the pathogenesis [4]. Paroxysms often start 5–7 days after injury, eventually starting earlier, and follow a regular pattern for several times a day. Diagnosis might be achievable quite early [5]. Each episode may last from less than 1 h to 10 h. It might be present from 1 week to several months. The diagnosis of paroxysmal sympathetic hyperactivity was proposed if four of six criteria are present in the absence of other potential causes [6]:

1. Fever (higher than 38.3 °C)
2. Tachycardia (heart rate more than 120 beats per minute or more than 100 beats per minute if the patient is treated with beta-blocker)
3. Hypertension (systolic blood pressure higher than 160 mmHg or pulse pressure higher than 80 mmHg)
4. Tachypnea (respiratory rate over 30 breaths per minute)
5. Excessive diaphoresis
6. Extensor posturing of extremitiesor severe dystonia

Infection needs to be excluded as well as epileptiform activity in EEG.

In addition to the management as presented later, morphine sulfate is effective to abort ongoing paroxysms.

7.3.2.2 Subarachnoid Hemorrhage

Profound sympathoexcitation is a common finding in subarachnoid hemorrhage [7]. ECG changes may occur, including elevation or depression of the ST segment, inverted or biphasic T waves, QTc prolongation, and even Q waves (see Fig. 7.2a–e). Troponin and creatine kinase might be increased. Abnormalities resolve within 1–4 days, whereas echocardiographic akinesia or hypokinesia might be present for weeks. Tachyarrhythmias are common.

Massive release of norepinephrine leads to myocardial damage, leading to subendocardial contraction band necrosis. Coronary artery disease is typically not present (see Fig. 7.2f). Neurogenic pulmonary edema might occur but might also be caused by vascular congestion.

7.3.3 Ischemic Insular Stroke

Strokes within the insular region can trigger excessive sympathetic activity, mounting in myocytolysis and arrhythmogenicity [8]. The lateralization was discussed, but similar complications are caused by strokes regardless of the side. Even more parietal lobe infarctions were identified as an increased risk for cardiac death and myocardial infarction [9, 10].

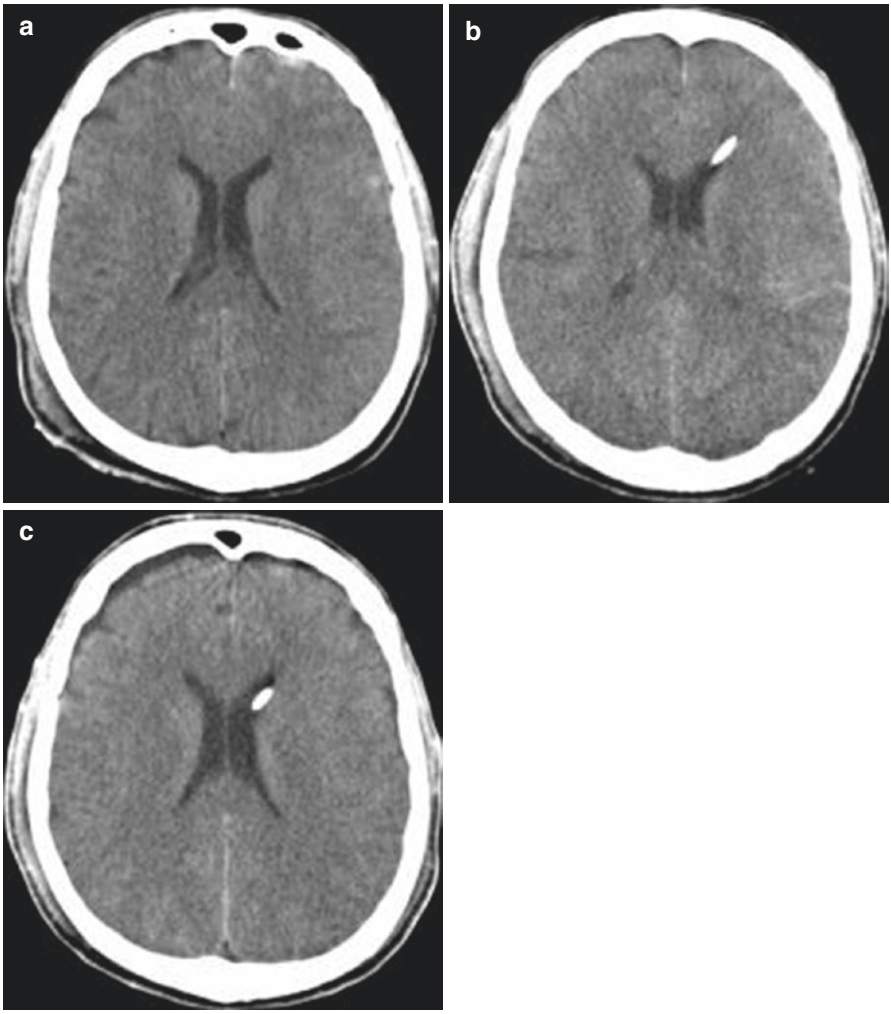

Fig. 7.2 (**a**–**c**) CT scan of a patient suffering severe traumatic subarachnoid hemorrhage and subdural frontal hematoma (dominated on the *right side*): (**a**) admission, (**b**) 6 h after admission, (**c**) 4d after admission. (**d**–**e**) ECG: admission (**d**) and day 5 (**e**). (**f**) Coronary angiography 63 minutes after detection of ECG changes, (**e**) no impeded coronary artery blood flow, no coronary artery disease

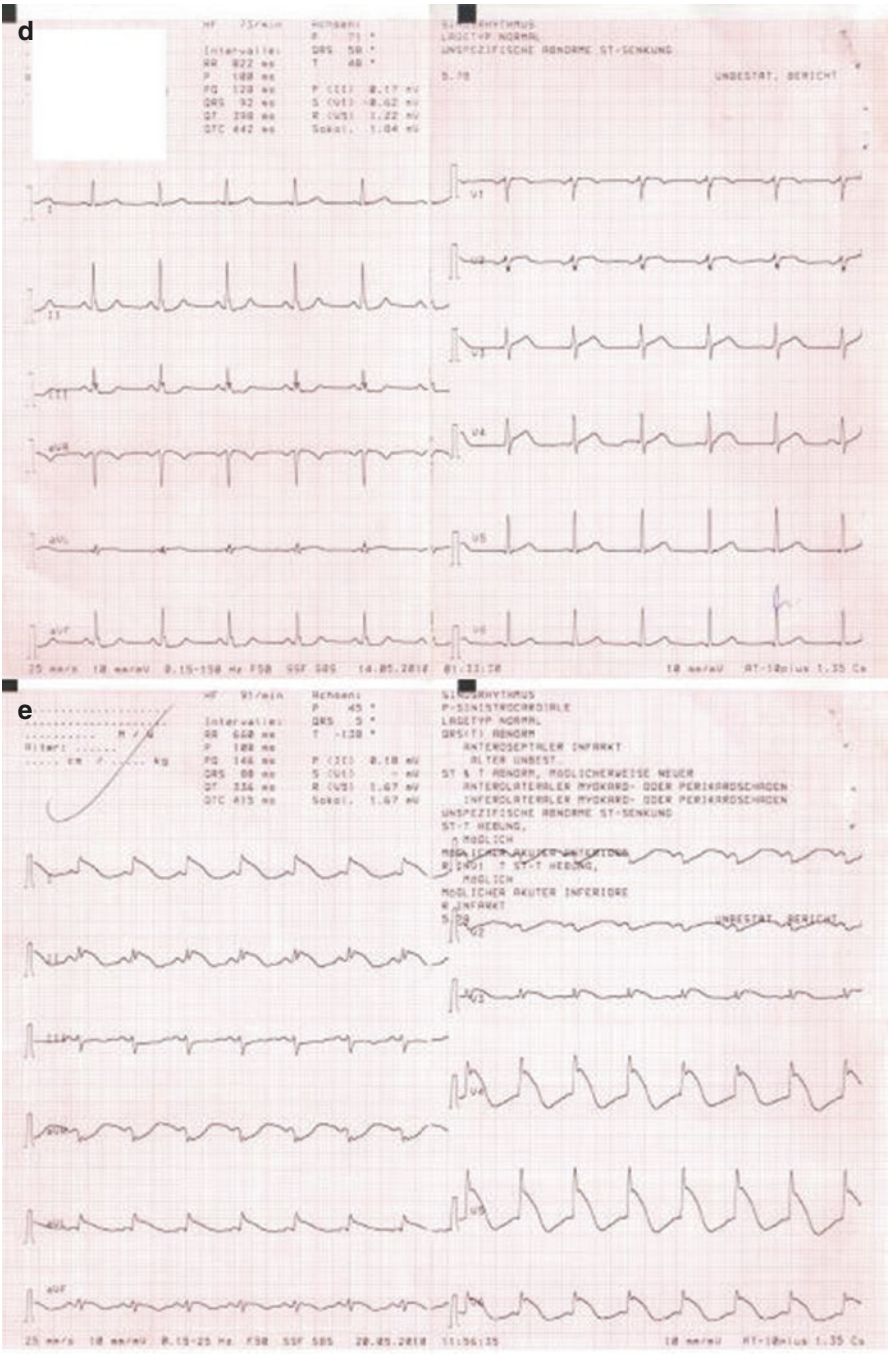

Fig. 7.2 (continued)

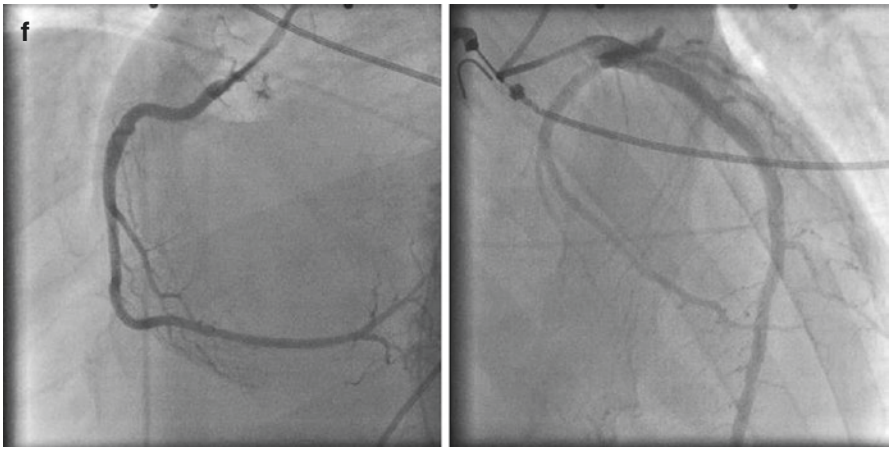

Fig. 7.2 (continued)

7.4 Management

Hypertension may be controlled by agents blocking sympathetic action. Alpha-blocker urapidil is valuable to sufficiently control blood pressure, eventually added by beta-blocking agents (e.g., metoprolol, labetalol, esmolol) or agents reducing central sympathetic outflow (clonidine). All those agents are given intravenously but clonidine, which is administered enterally to avoid the initial hypertensive response. Any medication that can increase intracranial pressure (calcium channel blockers, many vasodilators) is contraindicated. Avoid initially any long-acting oral medication as severe blood pressure fluctuations might occur. Reduce external and internal stimuli (pain, loud noises, endotracheal suctioning, or constipation).

Cardiac complications might be prevented by frequent electrolyte screening and early potassium and magnesium replacement if necessary. Sinus tachycardia sometimes might need treatment by beta-blockers as listed above. Cardiac arrhythmias should be treated as recommended in cardiologic guidelines. Atrial fibrillation or flutter may be treated with diltiazem or verapamil or digoxin loading, the latter being given especially in older patients. Amiodarone might achieve pharmacological cardioversion to sinus rhythm in atrial fibrillation but is demanded in sustained ventricular tachycardia. Reflex bradycardia should be avoided. Persisting bradycardia might be treated with atropine. Atrioventricular block second or third grade or recurring asystoles demand placement of a cardiac pacemaker.

7.4.1 Neurogenic Pulmonary Edema

Sudden development makes neurogenic pulmonary edema dangerous. Pulmonary venoconstriction and elevation of left-sided cardiovascular pressures might be contributing factors, as well as myocardial dysfunction. It might lead to profound hypoxemia.

Management In contrast to cardiogenic pulmonary edema, neurogenic pulmonary edema does not respond well to diuretics, if there is no cardiogenic component in addition. It is best treated by positive end-expiratory pressure and adequate oxygenation. It improves usually within 48 h, with resolution within 4–5 days.

7.4.2 Takotsubo Cardiomyopathy

Takotsubo syndrome is a cardiomyopathy mainly affecting the left ventricle [11]. Characteristic cardiac motion abnormalities are revealed in echocardiogram (transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical involvement; regional wall motion abnormalities beyond a single epicardial vascular distribution). There are no signs of coronary artery disease or angiographic evidence of acute plaque rupture. ST segment elevation and/or T-wave inversion in the electrocardiogram might mimic myocardial infarction; modest elevation in cardiac troponin might occur [12]. In acute phase, left ventricular ejection fraction might be severely reduced, and congested heart failure might be the consequence. Complete resolution within 2–4 weeks is often observed.

Management Main management strategies are supportive. There is so far no consensus on pharmacological treatment. Supportive treatment often leads to resolution of the condition. In the initial phase, aspirin or other antiplatelet agents are usually prescribed, although the benefit of this management is not clear. Cardiologic assistance systems are sometimes needed.

7.4.3 Noninfectious Fever

Noninfectious fever should only be suspected in those patients, who have no other causes of infection (including CNS). It occurs in direct lesions of the ventral hypothalamic thermoregulation (e.g., SAH, traumatic brain injury, encephalitis) or autonomic dysfunction in efferent projection to the sweat glands (GBS) or anticholinergic medication.

This is usually only seen in ICU patients, especially with SAH [13].

Management Antipyretic medication, physical cooling, invasive temperature regulation, eventually blockade of muscle activity.

7.4.4 Complications of Drugs Acting on Dopamine Receptors: Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is caused by D2 dopaminergic receptor blockade by psychiatric medication or sudden withdrawal of dopaminergic agonists in Parkinson's disease patients. Patients therefore have a psychiatric or movement disorder history. The risk to develop neuroleptic malignant syndrome is higher in

treatment with high-potency antipsychotics (e.g., haloperidol), or antiemetics (metoclopramide), also in atypical antipsychotic drugs (e.g., clozapine, olanzapine, risperidone, quetiapine, etc.) [2, 14]. Around 80% of the patients are under the age of 40, and males are twice as often affected as females. Patients with Lewy body disease might develop neuroleptic malignant syndrome at low antipsychotic doses already. Signs include tachycardia, labile blood pressure, hypersalivation, excessive sweating, fluctuations in the level of consciousness, pyrexia, and severe muscle rigidity. Laboratory evaluations show leukocytosis and elevated creatine kinase levels due to rhabdomyolysis.

Management Discontinue all antipsychotic medications, and possibly antidepressants, and lithium. Control body temperature by extra- or intracorporeal cooling, and monitor creatine phosphate kinase daily. Hypertension might respond to clonidine, and dantrolene or amantadine might be considered to control muscle tonus. Eventually muscle relaxants are needed such as dantrolene, although conflicting reports exist on the benefit of dantrolene. Benzodiazepine use had been reported, mainly to facilitate muscle relaxation.

7.4.5 Complications of Drugs Acting on Serotonin Receptors: Serotonin Syndrome

Symptoms are dose related and occur after administration of single or a combination of drugs acting on the serotonin receptors, particularly 5-HT2a (serotonin reuptake inhibitors like fluoxetine, paroxetine, sertraline, citalopram, etc.); 5-Ht1 agonists (e.g., triptans); monoamine oxidase inhibitors; opioids, valproate, lithium, antiemetic agents (metoclopramide, ondansetron), and cyclobenzaprine; and a number of drugs such as LSD and ecstasy [2]. Patients usually present in altered mental state (agitation, excitement, confusion) and show excessive profuse sweating, pyrexia, mydriasis, tachycardia, and tachypnea. Neuromuscular hyperactivity including tremor, clonus, myoclonus, and hyperreflexia might be present. Symptoms develop rapidly in 60% within 6 h of medication initiation, change in dosage, or overdosage [14]. In contrast to neuroleptic malignant syndrome in addition to clonus, diarrhea or hyperactive bowel sounds are typical symptoms.

Management Discontinue all serotoninergic medication. Control body temperature by extra- or intracorporeal cooling. Benzodiazepines might be beneficial for neuropsychiatric signs; eventually consider cyproheptadine, which acts as 5-HT2 antagonist.

7.4.6 Alcohol Withdrawal

Alcohol withdrawal may cause delirium tremens. Symptoms include confusion, anxiety, insomnia, tremor, hallucinations, and fluctuating psychomotor activity and usually appear 2 or 3 days after cessation of drinking. Sympathetic hyperactivity with hypertension, tachycardia, fever, diaphoresis, and flushing occurs [15].

Management Main treatment options are benzodiazepines, such as lorazepam. Dose should be individualized based on the symptoms. In severe cases, sedation at an intensive care unit is required.

7.4.7 Spinal Lesion: Acute Phase

In acute phase of spinal lesions, patients might suffer spinal shock with autonomic consequences.

Neurogenic shock is observed rather in higher lesions (20% of cervical, 3% of lumbar lesions); signs are reduced blood pressure and reduced heart rate.

Management Prevent vagal stimulation; prevent hypotonia (might lead to additional ischemia of the myelon); support therapy of bladder, gastric, or bowel atonia.

7.4.8 Spinal Lesion: Autonomic Dysreflexia

Autonomic dysreflexia in chronic stage of a spinal lesion is caused by reorganization of the spinal cord. It develops a month or more after the spinal lesion occurred. Determinants are the severity of the spinal lesion (incomplete or complete) and the level of the lesion, especially in relation to the major sympathetic outflow in lesions above T6. Potential stimuli, e.g., bladder and colonic distention, might induce autonomic activation: sympathetic activation below the level of spinal lesion with vasoconstriction (evident as dry, pale skin) and increased blood pressure. Secondary baroreceptor-mediated parasympathetic response above the lesion results in profuse sweating, piloerection, flushing, and bradycardia. These activations are mild to life threatening.

Management Prevent stimuli (especially the bladder); in acute hypertension, introduce blood pressure control: e.g., glyceryl trinitrate and nifedipine. In some patients, local anesthetics to the bladder might be considered.

7.4.9 Immune-Mediated Neuropathies: AIDP

In AIDP a number of autonomic complications are encountered. A sensitive early marker for autonomic complications is autonomic sinus tachycardia (> 100 /min). Persistent hypertension is common, likely based on reduced baroreflex function due to afferent neuropathy. Labile blood pressure (> 85 mmHg blood pressure fluctuation within a day systolic) is a prognostic marker for severe bradycardia [16]. Bradycardia occurs spontaneously or on vagal stimulation. Sudomotor changes are common with increased but also decreased sweating, often regional.

Management Patient with autonomic signs of AIDP have to be monitored. Hypertension should be treated only if sustained or secondary complications are present, due to the danger of labile blood pressure and severe hypotension. Tachyarrhythmias or vagally induced bradycardia might complicate the course. Eventually a pacemaker is needed. Bladder dysfunction and adynamic ileus are frequent complications.

Take home messages

Autonomic hyperactivities are severe life-threatening conditions, which require intensive management. Treatment is mainly symptomatic, eventually supported with a variable degree of sedation and stimulus deprivation. Stabilization of blood pressure, heart rate, and temperature is a challenge in these patients.

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References

1. Marthol H, Intravooth T, Bardutzky J, De Fina P, Schwab S, Hilz MJ (2010) Sympathetic cardiovascular hyperactivity precedes brain death. Clin Auton Res 20(6):363–369
2. Low PA, Benarroch EE, editors. Clinical autonomic disorders (2008) 3rd edn. philadelphia: Wolters Kluwer health/lippincott Williams & Wilkins
3. Sander D, Hilz MJ, Ziemssen T (2008) Autonome störungen. In: Schwab S, Schellinger P, Werner C, Unterberg A, Hacke W (eds) NeuroIntensiv. Springer, Heidelberg, pp 642–660
4. Hinson HE, Puybasset L, Weiss N, Perlbarg V, Benali H, Galanaud D et al (2015) Neuroanatomical basis of paroxysmal sympathetic hyperactivity: a diffusion tensor imaging analysis. Brain Inj 29:1–7
5. Hughes JD, Rabinstein AA (2014) Early diagnosis of paroxysmal sympathetic hyperactivity in the ICU. Neurocrit Care 20(3):454–459
6. Rabinstein AA, Benarroch EE (2008) Treatment of paroxysmal sympathetic hyperactivity. Curr Treat Options Neurol 10(2):151–157
7. Di Pasquale G, Andreoli A, Lusa AM, Urbinati S, Biancoli S, Cere E et al (1998) Cardiologic complications of subarachnoid hemorrhage. J Neurosurg Sci 42(1 Suppl 1):33–36
8. Goldstein DS (1979) The electrocardiogram in stroke: relationship to pathophysiological type and comparison with prior tracings. Stroke 10(3):253–259
9. Hilz MJ, Schwab S (2008) Stroke-induced sudden-autonomic death: areas of fatality beyond the insula. Stroke 39(9):2421–2422
10. Rincon F, Dhamoon M, Moon Y, Paik MC, Boden-Albala B, Homma S et al (2008) Stroke location and association with fatal cardiac outcomes: Northern Manhattan Study (NOMAS). Stroke 39(9):2425–2431
11. Yoshikawa T (2014) Takotsubo cardiomyopathy, a new concept of cardiomyopathy: Clinical features and pathophysiology. Int J Cardiol 182C:297–303
12. Roshanzamir S, Showkathali R (2013) Takotsubo cardiomyopathy a short review. Curr Cardiol Rev 9(3):191–196
13. Rabinstein AA, Sandhu K (2007) Non-infectious fever in the neurological intensive care unit: incidence, causes and predictors. J Neurol Neurosurg Psychiatry 78(11):1278–1280

14. Haddad PM, Dursun SM (2008) Neurological complications of psychiatric drugs: clinical features and management. Hum Psychopharmacol 23(Suppl 1):15–26
15. Mirijello A, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, Caputo F et al (2015) Identification and management of alcohol withdrawal syndrome. Drugs 75(4):353–365
16. Pfeiffer G, Schiller B, Kruse J, Netzer J (1999) Indicators of dysautonomia in severe Guillain-Barre syndrome. J Neurol 246(11):1015–1022

Recommended Further Reading

17. Clinical Autonomic Disorders – Evaluation and Management, ed. Phillip A. Low, Lippincot Ravens; Chapter 47

Sleep: Cardiovascular and Ventilatory Disorders

8

Luisa Sambati, Giovanna Calandra-Buonaura, and Pietro Cortelli

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8.1 Introduction

Sleep is regulated by brainstem and diencephalic structures interconnected with the autonomic nervous system (ANS) [1].

Sleep is associated with changes in ANS activity, and disorders of the ANS, in turn, affect vital functions during sleep. As a consequence of this interconnection, several neurologic disorders manifest with both autonomic dysfunctions and

L. Sambati • P. Cortelli (✉)
Department of Biomedical and NeuroMotor Sciences (DIBINEM) Alma Mater Studiorum, Università di Bologna, Ospedale Bellaria, Via Altura, 3, 40139 Bologna, Italy

IRCCS Istituto delle Scienze Neurologiche di Bologna, Ospedale Bellaria, Via Altura, 3, 40139 Bologna, Italy
e-mail: pietro.cortelli@unibo.it

G. Calandra-Buonaura
Department of Biomedical and NeuroMotor Sciences (DIBINEM) Alma Mater Studiorum, Università di Bologna, Ospedale Bellaria, Via Altura, 3, 40139 Bologna, Italy

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sleep disturbances, and sleep disorders [2] may be associated with or cause autonomic dysfunctions.

In particular disorders of cardiovascular and respiratory autonomic control during sleep have a negative prognostic role as they are associated with elevated risk of end-organ injury, to the heart, brain, and kidney [2, 3]. Therefore, an early detection of these disorders is mandatory to positively influence the disease course, guiding the appropriate therapy and risk factors' control.

This chapter describes sleep disorders [2–6] in which sleep disturbances and autonomic dysfunction develop following a common pathophysiological pathway (i.e., obstructive sleep apnea syndrome (OSAS) and narcolepsy type 1 (NT1)). Afterward, sudden unexpected death in epilepsy will be discussed as an example of disorders of cardiovascular and respiratory control during sleep associated with other neurological conditions.

For pathophysiology refer to Sect. 1.2.4.

8.2 Patient's History

A carefully history taking, assessing sleep disturbances including a detailed history of sleep habits, sleeps hygiene, and subjective sleep complaints, taken from the patient and his/her bed partner or caregiver is mandatory [5]. Additionally, assessing symptoms and signs of autonomic dysfunction and patient's comorbid illnesses and complete medical, family, and psychiatric history is valuable. Several clinical questionnaires could be used for the evaluation of both relevant autonomic and sleep symptoms and in order to assess the severity and distribution of symptoms [7]. Some useful questions may be found in Table 8.1. Furthermore, a detailed physical examination including the detection of BP response to upright posture is necessary when an autonomic dysfunction is suspected [8].

See for reference Sect. 2.2.5.

8.2.1 Diagnostic Workup

The gold standard for the diagnosis of a sleep disorder is polysomnography. This procedure allows the evaluation of multiple parameters and helps to assess cardiovascular and respiratory dysfunction of the autonomic control during sleep.

If a dysfunction of the autonomic control of the cardiovascular and respiratory system during sleep is suspected, the evaluation of 24-h BP profile could be made through 24-h ambulatory BP monitoring. This noninvasive technique could be

Table 8.1 Questions to interrogate sleep disorders

1. Have sleep habits changed? Duration, quality, onset of sleep, sleep interruptions, and nightmares?
2. Daytime sleepiness? Particularly in the morning? Afternoon naps?
3. Increase in blood pressure in the morning?
4. Questions for bed partner: Activity during sleep? Snoring?

useful to evaluate dipping profile at home during nighttime, but it is not conclusive because this procedure allows the evaluation of a single parameter only (Table 8.2, Fig. 8.1). If cardiorespiratory sleep disturbances are suspected, home testing with portable monitors (out-of-center sleep testing, OCST) is a well-accepted procedure. It is comfortable, reliable, and cost-effective. Airflow, respiratory effort, blood oxygenation (SpO2), and HR should be recorded (Table 8.2).

If an impairment of the autonomic control of the cardiovascular system is suspected, cardiovascular reflex tests should be performed, as described in Chap. 3.1 in detail [9–11].

Table 8.2 Laboratory assessment

Test	Outcome	Meaning
Cardiovascular		
Head-up tilt	No change in BP	Detection of OH
	Increased HR	Integrity of cardiac parasympathetic innervation
Valsalva maneuver	Normal changes in BP and HR	Integrity of baroreflex and cardiac parasympathetic innervation
Hyperventilation	Normal HR increase	Integrity of cardiac parasympathetic innervation
Cold face	Normal BP increase	Integrity of sympathetic outflow
Hand grip	Normal BP increase	Integrity of sympathetic outflow
Mental exercise	Normal BP increase	Integrity of sympathetic outflow
MIBG	Normal cardiac sympathetic innervation	Central lesion (as in normal subjects and MSA)
	Impaired cardiac sympathetic innervation	Distal impairment (as in PD, PAF, DLB)
24-h BP monitoring	>10% decrease in BP during sleep	Normal reduction in BP during sleep dipper pattern
	<10% decrease in BP during sleep	Loss of normal reduction in BP during sleep Non-dipper pattern Imbalance of sympathetic versus parasympathetic activity
Respiratory		
Cardiorespiratory monitoring	Sleep breathing dysfunctions	Detection of sleep breathing dysfunctions
		Staging of severity of sleep breathing dysfunctions
24-h videopolysomnography	Sleep pattern	Impairment of sleep structure
	Respiratory pattern	Detection of sleep breathing dysfunctions
	Blood pressure pattern	Impairment of the physiological circadian variation
	Temperature pattern	Impairment of the physiological circadian variation

BP blood pressure, *OH* orthostatic hypotension, *HR* heart rate, *HUT* head-up tilt test, *MIBG* cardiac radionuclide 123-meta-iodo-benzylguanidine imaging

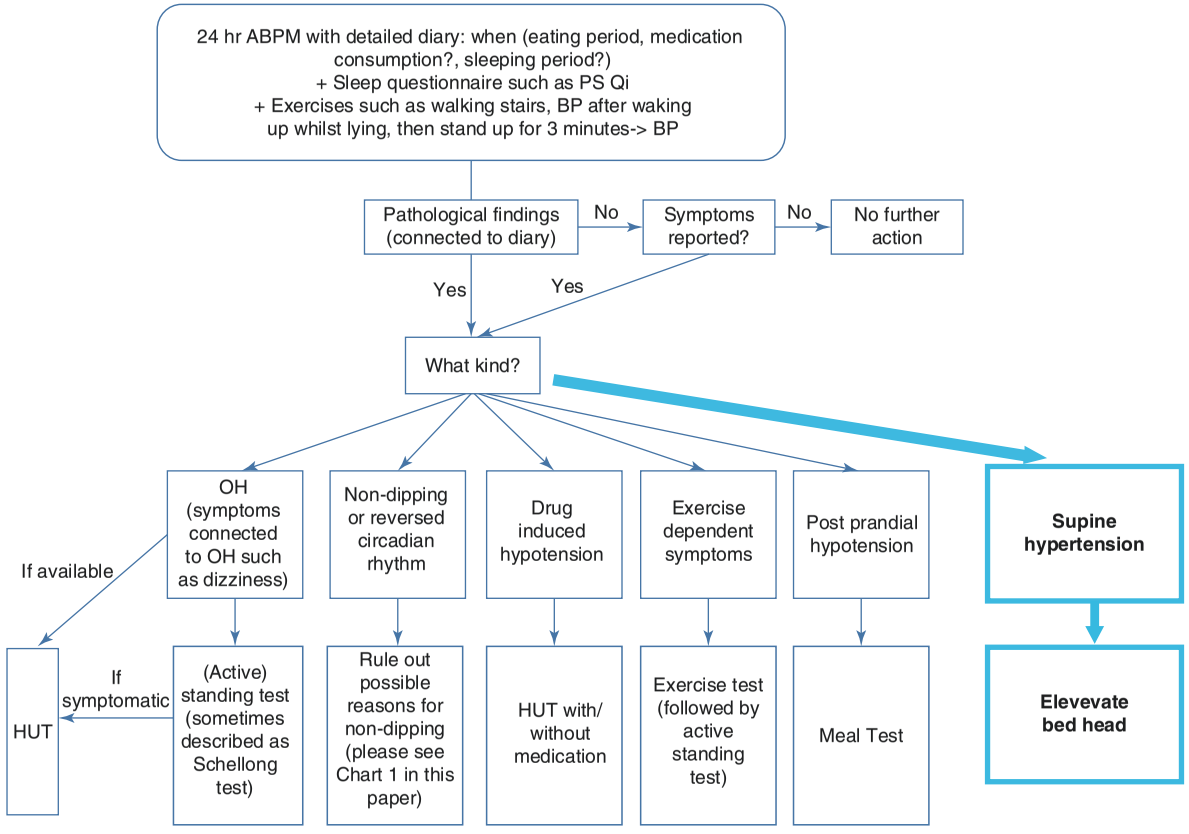

Fig. 8.1 Dysfunction of the autonomic control of the cardiovascular system, diagnostic algorithm. *24-h ABPM* ambulatory blood pressure monitoring, *OH* orthostatic hypotension, *HUT* head-up tilt test

8.3 Autonomic Disturbances and Sleep Disorders

8.3.1 Obstructive Sleep Apnea Syndrome Causing Cardiovascular Autonomic Dysfunction

Obstructive sleep apnea syndrome (OSAS) is the most common sleep breathing disorder with a prevalence of 2–4% in middle-aged population. According to the International Classification of Sleep Disorders, patients with OSAS complain about daytime sleepiness, non-restorative sleep, fatigue, or insomnia symptoms, including irritability and altered cognitive performance, and wake up with breath holding, gasping, or choking. In order to diagnose OSAS, the VPSG or the OCST should demonstrate at least five predominantly obstructive events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousal) per hour of sleep during a VPSG or per hour of monitoring.

The clinical relevance of OSAS is related to its strong association with obesity, hypertension, and increased cardiovascular risk [5, 6]. Recurrent apneas have three main effects: hypoxia and hypercapnia due to alterations in gas exchange, sleep fragmentation with repetitive arousal, and finally modification of sympathetic activity, with increased BP and HR. Although the pathophysiological factors linking OSAS and cardiovascular risk are not completely understood, several evidences support the hypothesis that sleep fragmentation and intermittent hypoxia during each apnoeic event cause a chronic hyperactivation of the sympathetic nervous system during both sleep and wakefulness. A further increase in sympathetic activity could be related to the depression of spontaneous baroreflex sensitivity (BRS) as a consequence of the arousal response. Furthermore, patients with OSAS may show a sinus brady-tachyarrhythmia during obstructive events, mediated by cyclical changes in parasympathetic and sympathetic neural activity. Compared to controls, OSAS patients are characterized by a lower total HRV and a possible shift of the sympatho-vagal balance toward a sympathetic predominance and a vagal withdrawal during wakefulness and sleep.

Undiagnosed sleep-disordered breathing might also play a role in the genesis of BP pattern alterations of some, if not all, non-dippers or even inverse dippers with essential hypertension (Fig. 8.1). This is more likely for male patients, since in the adult population snoring and OSAS are of much higher prevalence among men than women. Finally, tachyarrhythmia has been reported in patients with OSAS during hypoxic episodes and can be eliminated by oxygenation.

8.3.2 Narcolepsy Type 1

Narcolepsy type 1 is characterized by excessive daytime sleepiness, diagnosed as daily periods of irrepressible needs to sleep or daytime lapses into sleep occurring for at least 3 months, documented on a Multiple Sleep Latency Test (MSLT), and the presence of cataplexy [2]. It is often associated with sleep paralysis, hypnagogic hallucinations, and nocturnal sleep disruption [2].

Narcolepsy type 1 (NT1) is classified as hypersomnias of central origin, related to a loss of orexin signaling, due to loss of hypocretin containing neurons in the

hypothalamus. Hypocretin has been linked to various autonomic functions, such as cardiovascular, metabolic, thermoregulatory, and gastrointestinal regulation [12], although the contribution of loss of orexin signaling in these manifestations is not completely understood.

Regarding cardiovascular control, recent studies [12] indicate that daytime BP is comparable in patients with NT1 and controls, but patients with NT1 displayed a nighttime non-dipping BP pattern. The 24-h circadian rhythmicity of BP and HR is normal. Systolic BP during nighttime REM sleep is increased in the NT1 group. The altered nighttime BP regulation can be associated with an increased cardiovascular risk in NT1.

8.3.3 Sudden Unexpected Death in Epilepsy

Epilepsy is a brain disorder characterized by a predisposition to generate seizures, paroxysmal transient disturbances of brain functions that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, and psychic or sensory disturbances. Autonomic symptoms such as cardiovascular and respiratory changes and gastrointestinal, cutaneous, and genitourinary manifestations occur during epileptic seizures quite frequently [13].

In epileptic patients the risk of sudden unexpected death in epilepsy (SUDEP) is 24–40 times higher with respect to the general population. Clinical data suggest that SUDEP occurs preferentially during sleep. SUDEP is considered to be the result of a peri-ictal concurrence of a number of predisposing and precipitating factors. In particular, poor seizure control, high seizure frequency (especially generalized tonic-clonic seizures), brady- and tachyarrhythmia, onset of epilepsy at a young age, and long duration of epilepsy seem the most important risk factors. Both the absence of therapy and polytherapy represent further strong risk factors for SUDEP. Autonomic factors, in particular cardiac and respiratory dysfunctions, have been implicated in SUDEP.

Concerning cardiovascular autonomic dysfunction, decreased HRV is considered to be a risk factor for increased cardiovascular morbidity. Previous studies have indeed shown decreased HRV in chronic epileptic patients especially during nighttime in respect to control subject. Also, antiepileptic drugs, in particular carbamazepine and polytherapy, seem to reduce HRV. Seizures and periodic epileptic discharges, increasing arousal fluctuations leading to chronic sympathetic overactivation (e.g., increased BP and HR) during NREM sleep, might lead to a chronic stimulation of the ANS which is reflected by changes in HRV parameters.

8.3.4 Treatment

Considering the risk related to cardiovascular and respiratory dysfunction due to autonomic system alteration during sleep, it is crucial to find the optimal treatment and drug delivery formulations.

Supine hypertension is a common finding in cardiovascular dysregulation. A common approach to diminish supine hypertension is elevating the bed head about 20–30 cm. Please refer to Sect. 3.2.1.4. Reevaluation of pressure agents within the night hours helps to decrease supine hypertension.

The treatment of obstructive sleep apnea should be started with the treatment of the eventual comorbid disorder and with non-pharmacological measures, such as weight loss, exercise, sleep position, alcohol, and sedative avoidance. If the efficacy of these treatments is not satisfying, mechanical treatment with noninvasive continuous positive airway pressure (CPAP) ventilation that induces a low but significant reduction in 24-h blood pressure values should be promoted. If the patient is intolerant to CPAP, BiPAP should be considered.

Alternative treatment such as oral appliances (mandibular repositioning appliances, tongue-retaining devices) or bariatric surgery should also be considered. Surgical treatment is rarely curative but may improve clinical outcomes.

Considering SUDEP, a causative treatment is not feasible. Information and prevention are mandatory. A task force [13] proposed that every patient should know that epilepsy represents a condition with an increased risk of morbidity and death, in order to encourage development of coping strategies. First of all, adherence to several established principles in the treatment of epilepsy was recommended, in order to rapidly obtain a complete seizure control and to promptly identify patients with surgically remediable epilepsy. Night supervisor, positioning, use of anti-suffocation pillows, and stimulating the person seeking help if needed could be suggested to the patients and their caregivers. Furthermore, the treatment of sleep comorbidities, OSAS in primis, could reduce the occurrence of SUDEP.

Take-Home Messages

1. Sleep disorders [2] can be associated with cardiovascular and respiratory autonomic dysfunction occurring both during day and night. Several neurological disorders are associated with dysfunction of the autonomic cardiovascular and respiratory control during sleep [6–11].
2. Since cardiovascular and respiratory autonomic disturbances during sleep have a relevant impact on body homeostasis, detection of such disorders both during daytime and overnight is mandatory [14].
3. Autonomic dysfunction occurring during sleep, particularly when involving the cardiovascular or respiratory control, has a negative impact on the prognosis of the associated neurologic disorder [1, 4, 6]. A prompt diagnosis is therefore of crucial importance to choose the proper therapeutic approach and treat the risk factors that could severely influence disease prognosis.

References

1. Benarroch EE (ed) (1997) Central autonomic network: functional organization and clinical correlations. Futura Publishing Company, Armonk
2. American Academy of Sleep Medicine (AASM) (2014) The international classification of sleep disorders: diagnostic and coding manual, 3rd edn. American Academy of Sleep Medicine, Westchester
3. Boudreau P, Yeh WH, Dumont GA, Boivin DB (2013) Circadian variation of heart rate variability across sleep stages. Sleep 36(12):1919–1928. doi:10.5665/sleep.3230
4. Silvani A, Dampney RA (2013) Central control of cardiovascular function during sleep. Am J Physiol Heart Circ Physiol 305(12):H1683–H1692. doi:10.1152/ajpheart.00554.2013
5. Task Force of the American Academy of Sleep Medicine (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 5(3):263–276
6. Calandra-Buonaura G, Provini F, Guaraldi P, Plazzi G, Cortelli P. Cardiovascular autonomic dysfunctions and sleep disorders. Sleep Med Rev. 2015;3. pii: S1087–0792(15)00075–1. doi:10.1016/j.smrv.2015.05.005
7. Pierangeli G, Turrini A, Giannini G, Del Sorbo F, Calandra-Buonaura G, Guaraldi P, Bacchi Reggiani ML, Cortelli P (2015) Translation and linguistic validation of the composite autonomic symptom score COMPASS 31. Neurol Sci 36:1897–1902
8. Freeman R, Wieling W, Axelrod FB (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res: Off J Clin Auton Res Soc 21:69–72
9. Baschieri F, Calandra-Buonaura G, Doria A, Mastrolilli F, Palareti A, Barletta G, Solieri L, Guaraldi P, Martinelli P, Cortelli P (2015) Cardiovascular autonomic testing performed with a new integrated instrumental approach is useful in differentiating MSA-P from PD at an early stage. Parkinsonism Relat Disord 21(5):477–482. doi:10.1016/j.parkreldis.2015.02.011. Epub 2015 Feb 21
10. Corazza I, Barletta G, Guaraldi P, Cecere A, Calandra-Buonaura G, Altini E, Zannoli R, Cortelli P (2014) A new integrated instrumental approach to autonomic nervous system assessment. Comput Methods Programs Biomed 117(2):267–276. doi:10.1016/j.cmpb.2014.08.002
11. Sambati L, Calandra-Buonaura G, Doria A, Cortelli P (2015) Diagnosis and management of autonomic failure in neurodegenerative disorders. Eur Neurol 73(1–2):126–133. doi:10.1159/000368828
12. Grimaldi D, Silvani A, Benarroch EE, Cortelli P (2014) Orexin/hypocretin system and autonomic control: new insights and clinical correlations. Neurology 82:271–278
13. Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N (2013) Heart rate variability in normal and pathological sleep. Front Physiol 4:294. doi:10.3389/fphys.2013.00294
14. Cortelli P (2015) Chronomedicine: a necessary concept to manage human diseases. Sleep Med Rev 21:1–2. doi:10.1016/j.smrv.2015.01.005

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