24.14 Diseases of the autonomic nervous system 615

24.14 Diseases of the autonomic nervous system 6150 Christopher J. Mathias and David A. Low

ESSENTIALS The autonomic nervous system innervates all organs, producing predominantly involuntary and automatic actions that are medi- ated by two principal efferent pathways, the sympathetic and para- sympathetic, which are neurochemically and anatomically distinct. Numerous synaptic relays and neurotransmitters allow the auto- nomic control of organ function at local and central levels to be inte- grated with the requirements of the whole body. The peripheral and central components of the autonomic ner- vous system are frequently affected by diseases, conditions, or toxins. Autonomic disorders are described as (1) primary—without de- fined cause, including multiple system atrophy and acute/subacute dysautonomias; or (2) secondary—with specific defects or as a con- sequence of other conditions, including diabetes mellitus, Riley–Day syndrome, amyloid neuropathy, dopamine β-hydroxylase deficiency, spinal cord injury, and many drugs. Clinical features Failure of the autonomic nervous system—manifestations may be (1) sympathetic—adrenergic failure causes postural (orthostatic) hypotension and (in men) disturbed ejaculation; cholinergic disturb- ances interfere with sweating; (2) parasympathetic—causing a fixed heart rate, erectile failure, and disturbed emptying of the urinary bladder and large intestine. Overactivity of the autonomic nervous system—manifestations may be (1) sympathetic—characterized by hypertension, tachycardia, and excessive sweating; (2) parasympathetic—leading to bradycardia. Mixed effects, peripherally and centrally, lead to

complex clinical manifestations. Investigation Autonomic screening tests include (1) cardiovascular—(a) physio- logical (e.g. head-up tilt, heart rate responses), (b) biochemical (e.g. plasma noradrenaline, adrenaline, and dopamine levels), (c) pharma- cological (e.g. clonidine growth hormone stimulation); (2) sweating (e.g. thermoregulatory response to increasing core temperature by 1°C). Autonomic dysfunction may also be suggested by a wide var- iety of other tests, including those of gastrointestinal, urinary/renal, sexual, respiratory, and eye function. Treatment Symptomatic—(1) Orthostatic hypotension—management requires an approach combining (a) nonpharmacological measures (e.g. avoidance of sudden standing, high salt intake); and (b) pharmaco- logical measures (e.g. fludrocortisone, sympathomimetics, such as ephedrine or midodrine). (2) Other symptoms—combined pharma- cological and physical interventions can improve urinary incontin- ence, gastrointestinal motility disorders, and sexual dysfunction. Care is required to manipulate autonomic activity in patients with parkin- sonian manifestations because the autonomic aspects are frequently exacerbated by antiparkinsonian agents. Specific—some causes of autonomic dysfunction are treatable (e.g. infusions of immunoglobulin and plasmapheresis for immune- mediated neuropathy); hepatic transplantation in familial amyloid polyneuropathy. Introduction The autonomic nervous system has two principal efferent path- ways, sympathetic and parasympathetic, that innervate and influ- ence every organ in the body (Fig. 24.14.1). Autonomic actions are predominantly involuntary and automatic, as indicated by the term ‘autonomic’ first proposed by Langley in 1898. The structure of the autonomic system, with numerous synapses centrally and periph- erally, as well as multiple neurotransmitters, provides flexible con- trol of organ function locally and in an integrated manner—as in the maintenance of systemic blood pressure and body temperature. Disease of the autonomic nervous system may cause local or sys- temic effects. Basic principles The autonomic nervous system is primarily a visceromotor system, in which each efferent pathway is influenced in a variety of ways. Feedback and central integration are important and virtually every sensory pathway can influence its activity. For example, in spinal cord lesions, activation of visceral, skin, and muscle receptors below the level of the lesion influences autonomic activity and blood pres- sure through the spinal pathways, while heart rate responses to 24.14 Diseases of the autonomic
nervous system Christopher J. Mathias and David A. Low

24.14 Diseases of the autonomic nervous system 6151 classic afferent baroreceptor pathways are retained. Key cerebral autonomic centres are in the hypothalamus, midbrain (Edinger– Westphal nucleus and locus ceruleus), and brain stem (nucleus tractus solitarius and vagal nuclei), and through intracerebral con- nections. Many other areas affect autonomic activity. Examples are the insular cortex, anterior cingulate gyrus, and amygdala, which are important in processing emotion and autonomic effects. Parasympathetic efferent pathways are craniosacral and sympathetic efferents are thoracolumbar; each has pre- and postganglionic fibres. The sympathetic ganglia are placed further from target organs than the parasympathetic ganglia. Autonomic nerve terminals at target organs vary in complexity; they have the capacity to synthesize neurotransmitters and a host of mechanisms affects uptake and interaction with local or blood- borne chemicals (Fig. 24.14.2). There are differences between or- gans, especially the gastrointestinal system, in which the enteric nervous system is considered as a third autonomic division. The multiplicity of neural pathways, transmitters, and modulators re- sults in selective control of responses in specific vascular territories and organs, making it a highly complex but precisely regulated and integrated system. Classification Diseases of the autonomic nervous system may result in central or peripheral damage or derangement; these may be primary with no known cause or secondary with

specific abnormalities (dopamine β-hydroxylase deficiency), or strong associations with other diseases (Holmes–Adie syndrome or diabetes mellitus) (Table 24.14.1). Intermittent autonomic dysfunction may cause cardiovascular or sudomotor abnormalities (autonomic (neurally) mediated syn- cope or primary hyperhidrosis) (Box 24.14.1). Drugs are a common cause of autonomic dysfunction (Box 24.14.2). Classification can be considered in various ways. Dysfunction may be localized (Box 24.14.3) or widespread. Diseases may re- sult from lesions that are central (multiple system atrophy), spinal (spinal cord transection), or peripheral (pure autonomic failure), or from a highly specific biochemical deficit (dopamine β-hydroxylase deficiency). Some are age related, with presentation at birth (Riley– Day syndrome), second decade (autonomic mediated syncope), or adulthood (familial amyloid polyneuropathy). Autonomic failure commonly causes underactivity, but the reverse, overactivity, can cause various manifestations, for example, paroxysmal hyperten- sion during autonomic dysreflexia in high spinal cord injuries. In autonomic mediated syncope there may be a combination of vagal overactivity and/or sympathetic withdrawal. Clinical features Sympathetic adrenergic failure causes orthostatic hypotension and ejaculatory failure in men, while sympathetic cholinergic failure causes anhidrosis. Parasympathetic failure results in a fixed heart Sympathetic nervous system Mesen- cephalon Pons Superior cervical ganglion Stellate ganglion Coeliac ganglion Sympathetic trunk Superior mesenteric ganglion Inferior mesenteric ganglion Tear and salivary glands Liver Eye Lung Heart Stomach Pancreas Small intestine Large intestine rectum Bladder Reproductive organs Parasympathetic nervous system Vagus n. Cervical Thoracic Lumbar Sacral III IX.VII X Medulla obl. Fig. 24.14.1 Sympathetic (thoracolumbar) and parasympathetic (cranial and sacral) pathways that innervate a variety of organs. From Schmidt RF, Lang F (eds) (2007). Physiologie des Menschen, 30th edition. Springer-Verlag, Heidelberg. Copyright © 2007, Springer Medizin Verlag Heidelberg, with permission of Springer.

section 24 Neurological disorders 6152 Table 24.14.1 Classification of disorders resulting in autonomic dysfunction Primary (aetiology unknown) Acute/subacute dysautonomias Pure pandysautonomia Pandysautonomia with neurological features Pure cholinergic dysautonomia Chronic autonomic failure syndromes Pure autonomic failure Multiple system atrophy (Shy–Drager syndrome) Autonomic failure with Parkinson’s disease Secondary Congenital Nerve growth factor deficiency Hereditary Autosomal dominant trait Familial amyloid neuropathy Porphyria Autosomal recessive trait Familial dysautonomia (Riley–Day syndrome) Dopamine β-hydroxylase deficiency Aromatic l-amino acid decarboxylase deficiency X-linked recessive Fabry’s disease Metabolic diseases Diabetes mellitus Chronic renal failure Chronic liver disease Vitamin B12 deficiency Alcohol induced Inflammatory Guillain–Barré syndrome Transverse myelitis Infections Bacterial Tetanus, leprosy Viral HIV infection Parasitic Chagas’ disease Prion Fatal familial insomnia Neoplasia Brain tumours—especially of the third ventricle or posterior fossa Paraneoplastic, to include adenocarcinomas of lung and pancreas, and Lambert–Eaton syndrome Connective tissue disorders Rheumatoid arthritis Systemic lupus erythematosus Mixed connective tissue disease Surgery Regional sympathectomy—upper limbs, splanchnic denervation Vagotomy and drainage procedures—‘dumping syndrome’ Organ transplantation—heart, kidney Trauma Spinal cord transection Miscellaneous Subarachnoid haemorrhage Syringobulbia and syringomyelia Intermittent autonomic dysfunction See Box 24.14.1 Drugs See Box 24.14.2 From Mathias (2009).

(a) Sympathetic nerve terminal Effector cell COMT Tyrosine Synaptic cleft Uptake 2 Uptake 1 TH DOPA DDC DA NA MAO + − D H D H (b) Ganglia Parasympathetic Sympathetic ACh-n ACh-m (VIP) NA (NPY) Glands Smooth muscle Heart ACh-m Blood vessels Heart Sweat glands DA − + NA Sympathetic ACh-n ACh-n NA − Target organ 2 1 Fig. 24.14.2 Schema of some pathways in the formation, release, and metabolism of noradrenaline from sympathetic nerve terminals. Tyrosine is converted into dihydroxyphenylalanine (dopa) by tyrosine hydroxylase (TH). Dopa is converted into dopamine (DA) by dopa-decarboxylase (DDC). In the vesicles, dopamine is converted into noradrenaline (NA) by dopamine β-hydroxylase. Nerve impulses release both dopamine β-hydroxylase and noradrenaline into the synaptic cleft by exocytosis. Noradrenaline acts predominantly on α1-adrenoceptors but has actions on β-adrenoceptors on the effector cell of target organs. It also has presynaptic adrenoceptor effects. Those acting on α2-adrenoceptors inhibit noradrenaline release and those on β-adrenoceptors stimulate noradrenaline release. Noradrenaline may be taken up by a neuronal process (uptake 1) into the cytosol, where it may inhibit further formation of dopa through the rate-limiting enzyme tyrosine hydroxylase. Noradrenaline may be taken into vesicles or metabolized by monoamine oxidase (MAO) in the mitochondria. Noradrenaline may be taken up by a higher-capacity, but lower-affinity, extraneuronal process (uptake 2) into peripheral tissues, such as vascular and cardiac muscle and certain glands. Noradrenaline is also metabolized by catechol-O-methyl transferase (COMT). Thus, noradrenaline measured in plasma is the overspill not affected by these numerous processes. (b) Outline of the major transmitters at autonomic ganglia and postganglionic sites on target organs supplied by the parasympathetic and sympathetic efferent pathways. The acetylcholine (ACh) receptor at all ganglia is of the nicotinic subtype (ACh-n). Ganglionic blockers such as hexamethonium thus prevent both parasympathetic and sympathetic activation. Atropine, however, acts only on the muscarinic (ACh-m) receptors at postganglionic parasympathetic and sympathetic cholinergic sites. The cotransmitters, along with the primary transmitters, are also indicated. NPY, neuropeptide Y; VIP, vasoactive intestinal peptide. (a) From Mathias CJ (2004). Disorders of the autonomic nervous system. In: Bradley WG, Daroff RB, Fenichel GM, Jancovich J (eds) Neurology in Clinical Practice, 4th edition. Butterworth-Heinemann, Boston, USA, 2403–40. (b) From Mathias CJ (1998). Autonomic disorders. In: Bogousslavsky J, Fisher M (eds) Textbook of Neurology. Butterworth-Heinemann, Massachusetts, pp. 519–45.

 rate, a sluggish urinary bladder and large bowel, and, in men, erectile dysfunction. With overactivity there may be hypertension, tachy- cardia, and hyperhidrosis, although parasympathetic overactivity causes bradycardia. In autonomic disorders there are many clinical manifestations, which may cause diagnostic difficulties, especially when the disorder is generalized. The presenting complaints often provide clues. Palmar hyper hidrosis or gustatory sweating may indicate a localized disorder, or be a harbinger of widespread autonomic impairment, as the latter may complicate diabetes mellitus. A cardinal feature is orthostatic hypotension (defined as a decrease in systolic blood pressure of more than 20 mm Hg and/or in diastolic pressure of more than 10 mm Hg on standing or head-up tilt—Fig. 24.14.3); this impairs perfusion of vital organs such as the brain. The symp- toms vary from fainting (syncope, loss of consciousness), some- times with ensuing injury, to fatigue and lethargy. Numerous factors in daily life enhance or reduce hypotension (Box 24.14.4). Some patients recognize these, with the self-introduction of cor- rective measures. Large meals, refined carbohydrate, and alcohol, which enhance postprandial hypotension, are avoided. Many sit down, lie flat, or assume curious postures, such as squatting or stooping, which now are recognized as raising blood pressure (Fig.

24.14.4). With time, symptoms of orthostatic hypotension wane, for reasons such as improved cerebrovascular autoregula tion. In autonomic mediated syncope, venepuncture, or pain (in vasovagal syncope) or cervical movements and pressure (in carotid sinus hypersensitivity) cause hypotension and bradycardia. A his- tory of impaired sweating and temperature intolerance, urinary disturbances, sexual dysfunction (in men), and gastrointestinal derangement (constipation), especially together with orthostatic hypotension, should suggest a generalized autonomic disorder (Table 24.14.2). In the Riley–Day syndrome (familial dysautonomia) there is a his- tory of consanguinity, usually in the Ashkenazi Jewish population. A family history is often elicited in the vasovagal form of autonomic mediated syncope and expected in familial amyloid polyneuropathy. A drug history, including exposure to chemicals, toxins, and poi- sons, is important. Box 24.14.1 Intermittent autonomic dysfunction • Autonomic (neurally) mediated syncope — Vasovagal syncope — Carotid sinus hypersensitivity — Situational syncope — Micturition syncope — Swallow syncope — With glossopharyngeal neuralgia — Defecation syncope — Laughter-induced syncope • Postural tachycardia syndrome • Initial orthostatic hypotension • Primary or essential hyperhidrosis Box 24.14.2 Drugs, chemicals, poisons, and toxins causing autonomic dysfunction Decreasing sympathetic activity Centrally acting • Clonidine • Methyldopa • Moxonodine • Reserpine • Barbiturates • Anaesthetics Peripherally acting • Sympathetic nerve endings (guanethidine, bethanidine) • α-Adrenoceptor blockade (phenoxybenzamine) • β-Adrenoceptor blockade (propranolol) Increasing sympathetic activity • Amphetamines • Releasing noradrenaline (tyramine) • Uptake blockers (imipramine) • Monoamine oxidase A inhibitors (tranylcypromine) • β-Adrenoceptor stimulants (isoprenaline) Decreasing parasympathetic activity • Antidepressants (imipramine) • Tranquillizers (phenothiazines) • Antidysrhythmics (disopyramide) • Anticholinergics (atropine, probanthine, benzatropine) • Toxins (botulinum) Increasing parasympathetic activity • Cholinomimetics (carbachol, bethanechol, pilocarpine, mushroom poisoning) • Anticholinesterases • Reversible carbamate inhibitors (pyridostigmine, neostigmine) • Organophosphorus inhibitors (parathion, sarin) Miscellaneous • Alcohol, thiamine (vitamin B deficiency) • Vincristine, perhexiline maleate • Thallium, arsenic, mercury • Mercury poisoning (‘pink’ disease) • Ciguatera toxicity • Jellyfish and marine animal venoms • First-dose effects of drugs (prazosin, captopril) • Withdrawal of chronically used drugs (opiates, clonidine, alcohol) Adapted from Mathias (2009). Box 24.14.3 Examples of localized autonomic disorders • Holmes–Adie pupil • Horner’s syndrome • Crocodile tears (Bogorad’s syndrome) • Gustatory sweating (Frey’s syndrome) • Reflex sympathetic dystrophy • Idiopathic palmar/axillary hyperhidrosis • Chagas’ diseasea Surgical proceduresb • Sympathectomy—regional • Vagotomy and gastric drainage procedures in ‘dumping syndrome’ • Organ transplantation—heart, lungs a Listed here because it targets intrinsic cholinergic plexus in the heart and gut. b Surgery may cause some of the disorders listed here such as Frey’s syndrome after parotid surgery. From Mathias (2009).

 A detailed clinical examination is necessary. Pupillary and as- sociated ocular abnormalities occur in Horner’s syndrome. To as- sess orthostatic hypotension, blood pressure should be measured with the patient lying flat, and after standing (or sitting, if not possible). A fall in systolic blood pressure of less than 20 mm Hg in the presence of appropriate symptoms does not exclude auto- nomic failure. Indeed, orthostatic hypotension may be unmasked, or enhanced, by factors such as ingestion of food and/or exercise. Furthermore, in the presence of vascular disease (such as carotid artery stenosis) even a small fall in blood pressure results in cere- bral ischaemia. Lack of additional neurological features favours pure autonomic

failure (with a good prognosis), while associated parkinsonism or cerebellar dysfunction suggests multiple system atrophy. Several disorders causing a peripheral neuropathy result in autonomic impairment. Basic bedside testing for glycosuria (in diabetes mellitus) or proteinuria (in systemic amyloidosis) provides important information. Investigations When an autonomic disorder is suspected, the first step is to de- termine if autonomic function is normal or abnormal. Autonomic screening tests (Box 24.14.5) have their value, but also their 160 (a) (b) (c) 140 120 100 80 60 40 20 200 150 100 50 160 140 120 100 80 60 40 20 200 150 100 160 140 120 100 80 60 40 20 200 150 100 50 0 16:00 20:00 24:00 04:00 08:00 12:00 16:00 Blood Pressure (mm Hg) Heart Rate (beat min–1) Blood Pressure (mm Hg) Heart Rate (beat min–1) Blood Pressure (mm Hg) Heart Rate (beat min–1) 0 50 0 0 0 0 Box 24.14.4 Factors influencing orthostatic hypotension • Speed of positional change • Time of day (worse in the morning) • Prolonged recumbency • Warm environment (hot weather, central heating, hot bath) • Raising intrathoracic pressure: micturition, defecation, or coughing • Food and alcohol ingestion • Water ingestiona • Physical exertion • Manoeuvres and positions (bending forward, abdominal com- pression, leg crossing, squatting, activating calf muscle pump)b
(Fig. 24.14.5) • Drugs with vasoactive properties (including dopaminergic agents) a Raises supine blood pressure in chronic autonomic failure. b These manoeuvres usually reduce the postural fall in blood pressure, unlike the others. Adapted from Mathias et al. (2013). Fig. 24.14.3 Twenty-four hour noninvasive ambulatory blood
pressure profiles, showing systolic and diastolic blood pressure and heart rate at intervals through the day and night (the black bars indicate periods when the patient was in bed). (a) The changes in a normal subject with no postural fall in blood pressure; there was a fall in blood pressure at night while asleep, with a rise in blood pressure on waking. (b) The marked variability in heart rate in a patient with the postural tachycardia syndrome. The profile indicates episodes of profound tachycardia without hypotension. (c) The marked fluctuations in blood pressure in a patient with pure autonomic failure. The marked falls in blood pressure are usually the result of postural changes, either sitting or standing. Supine blood pressure, particularly at night, is elevated. Getting up to micturate causes a marked fall in blood pressure (at 03:00 hours). There is a reversal of the diurnal changes in blood pressure. There are relatively small changes in heart rate, considering the marked changes in blood pressure.

 limitations. The majority are directed towards cardiovascular as- sessment and exclusion of autonomic underactivity. Tests of other systems are increasingly being made available. Normal screening results do not necessarily exclude an autonomic disorder, because, on the basis of the history and clinical examination, additional tests, such as carotid sinus massage may be needed in patients with syncope. If autonomic tests are abnormal, further evaluation will determine the site and extent of the autonomic lesion, the func- tional deficit, and whether it results from a primary or secondary disorder, because an accurate diagnosis is essential for prognosis and appropriate management. A 24-h ambulatory blood pres- sure and heart rate profile using the autonomic protocol that in- cludes the effects of stimuli in daily life (such as food and exercise; Fig. 24.14.3) help in the evaluation and management of disorders 60° HEAD-UP TILT Normal Blood pressure (a) (b) (c) mmHg Heart rate bpm 60° Head up tilt Heart rate bpm 180 150 Blood pressure mmHg Autonomic failure 60° HEAD-UP TILT 150 180 0 0 0 0 Heart rate bpm Blood pressure mmHg Spinal injury 3 MIN OF 60° HEAD-UP TILT 150 180 0 0 Fig. 24.14.4 (a) Continuous blood pressure and heart rate recorded noninvasively before, during, and after head-up tilt in a normal individual (upper panel),

and (b) in a patient with autonomic failure and (c) in a patient with a high cervical spinal cord lesion. In the normal individual there is no fall in blood pressure during head-up tilt, unlike a patient with autonomic failure in whom blood pressure falls promptly and remains low with a blood pressure overshoot on return to the horizontal. In this patient there is only a minimal change in heart rate despite the marked blood pressure fall. In the patient with spinal cord injury there is a fall in blood pressure because of impairment of the sympathetic outflow disrupted in the cervical spine. Heart rate rises because of withdrawal of vagal activity in response to the rise in pressure. (a) Adapted from Mathias CJ (2015). Orthostatic hypotension and orthostatic intolerance. In: De Groot JL,
Jameson LJ (eds) Endocrinology, 7th edition. Elsevier, Philadelphia, PA. (b) From Mathias CJ (2015). Orthostatic hypotension and orthostatic intolerance. In: De Groot JL, Jameson LJ (eds) Endocrinology, 7th edition, Elsevier, Philadelphia, PA.

section 24 Neurological disorders 6156 such as orthostatic hypotension and postural tachycardia syn- drome. Plasma catecholamine (noradrenaline and adrenaline, and in rare disorders such as dopamine β-hydroxylase deficiency, dopamine) measurements (Fig. 24.14.6) and the clonidine growth hormone stimulation test may separate out the different auto- nomic failure syndromes. Investigations may be needed to diag- nose underlying diseases, and include neuroimaging studies (MRI or CT, MNR angiogram), serum amyloid protein scans, sural nerve Table 24.14.2 Some of the clinical manifestations and possible presentations in primary chronic autonomic failure syndromesa Cardiovascular Orthostatic hypotension Sudomotor Anhidrosis, heat intolerance Gastrointestinal Constipation, occasionally diarrhoea,
oropharyngeal dysphagia Renal and urinary
bladder Nocturia, frequency, urgency, incontinence, retention Sexual Erectile and ejaculatory failure in men Ocular Aniscoria, Horner’s syndrome Respiratory Stridor, involuntary inspiratory gasps, apnoeic episodes Other neurological deficits Parkinsonian and cerebellar/pyramidal features a Certain features, such as oropharyngeal dysphagia and respiratory abnormalities (including those resulting from laryngeal fold paresis), occur in multiple system atrophy rather than in pure autonomic failure. From Mathias (2009). Box 24.14.5 Autonomic disorders considered
under prognosis and response to intervention • Fixed and irreversible—pure autonomic failure (PAF), spinal cord injury • Progressive and irreversible—multiple system atrophy (MSA) • Progressive but stoppable—familial amyloid polyneuropathy, dia- betes mellitus • Reversible—immune-mediated autonomic neuropathy 200 0 200 0 200 0 0 120 Time (sec) 0 0 120 60 Time (sec) Time (sec) BP (mmHg) 200 0 0 120 Time (sec) BP (mmHg) BP (mmHg) BP (mmHg) Fig. 24.14.5 Physical countermanoeuvres using isometric contractions of the lower limbs and abdominal compression. The effects of leg crossing in standing and sitting position, placing a foot on a chair and squatting on finger arterial blood pressure in a 54-year- old man with pure autonomic failure and incapacitating orthostatic hypotension. The patient was standing (sitting) quietly prior to the manoeuvres. Bars indicate the duration of the manoeuvres. Note the increase in blood pressure and pulse pressure during the manoeuvres. From Wieling W et al. (2004). Non-pharmacological treatment of reflex syncope. Clin Auton Res, 14 (Suppl 1), 62–70. Copyright © 2004, Steinkopff Verlag, with permission of Springer.

 biopsy (with specific staining with monoclonal antibodies), de- tection of antibodies to specific receptors (such as the nicotinic acetylcholine receptor), and genetic testing. These tests should be combined with nonneurological

investigations, depending on the suspected diagnosis. Treatment This varies depending on the autonomic disease, the systems af- fected and the functional autonomic deficit, and whether the disorder is primary or secondary. Treatment should consider the underlying condition (e.g. in parkinsonian syndromes), where autonomic features may be worsened by antiparkinsonian therapy. In some diseases simple intervention is effective, such as unblocking a urinary catheter to resolve autonomic dysreflexia in high spinal cord lesions. In some, immunological therapy (intravenous γ-globulin, plasma exchange) can reverse the auto- nomic neuropathy. Complex procedures such as liver trans- plantation are needed to reduce variant transthyretin levels in familial amyloid polyneuropathy. Multidisciplinary expertise may be needed, as in the Riley–Day syndrome and multiple system atrophy, to prevent complications, enhance survival, and improve quality of life. A combined approach is needed to reduce orthostatic hypotension, overcome urinary incontin- ence, alleviate gastrointestinal disturbances, and treat sexual dysfunction. The management of orthostatic hypotension is outlined in Box 24.14.6 and Table 24.14.3; in individual disorders, modifi cation is needed. In intermittent autonomic disorders the treatment varies, depend ing on the pathophysiological processes. Advances in the recognition, understanding of the patho- physiological changes, and treatment of autonomic disorders continue to progress. This relates also to disorders resulting in damage to the autonomic nervous system, examples of which are provided next and considered under prognosis based on the natural history of the disorder and/or possible interventional measures (Box 24.14.4). In spinal cord injury, the possibility of reversal has recently been raised, unlike pure autonomic failure and mul- tiple system atrophy. Autonomic involvement in familial amyloid polyneuropathy is usually relentless but can be halted by liver transplantation and possibly drugs, as can autonomic neur- opathy in diabetes mellitus. Autonomic deficits can be substanti ally reversed in some with an immune-mediated autonomic neuropathy. 0 Noradrenaline (pg/ml) Adrenaline (pg/ml) SUPINE 500 400 600 200 100 Dopamine (pg/ml) TILT 300 600 500 400 300 200 100 0 600 500 400 300 200 100 0 DBH defn-2 DBH defn-1 PAF MSA Controls DBH defn-2 DBH defn-1 PAF MSA Controls DBH defn-2 DBH defn-1 PAF MSA Controls * * * * Fig. 24.14.6 Plasma noradrenaline, adrenaline, and dopamine concentrations (measured by high-performance liquid chromatography) in normal individuals (controls), patients with multiple system atrophy (MSA), patients with pure autonomic failure (PAF), and two individual patients with dopamine β-hydroxylase deficiency (DβH defn) while supine and after head-up tilt to 45° for 10 min. The asterisk indicates levels below the detection limits for the assay, which are less than 5 pg/ml for noradrenaline and adrenaline and less than 20 pg/ml for dopamine. Bars indicate ± standard error of the mean. Adapted from Mathias CJ, Low DA, Bannister R (2013). Investigation of autonomic disorders. In: Mathias CJ, Bannister R (eds) A Textbook of Clinical Disorders of the Autonomic Nervous System, 5th edition. Oxford University Press, Oxford. Box 24.14.6 Outline of nonpharmacological and pharmacological measures in the management of postural hypotension due to neurogenic failure Nonpharmacological measures To be avoided • Sudden head-up postural change (especially on waking) • Prolonged recumbency • Straining during micturition and defecation • High environmental temperature (including hot baths) • ‘Severe’ exertion • Large meals (especially with refined carbohydrate) • Alcohol • Drugs with vasodepressor properties To be introduced • Head-up tilt during sleep • Small, frequent meals • High salt intake • Judicious exercise (including swimming) • Body positions and manoeuvres To be considered • Water ingestion • Elastic stockings • Abdominal binders Pharmacological measures • Starter drug—fludrocortisone • Sympathomimetics—ephedrine, midodrine or DL-DOPS/L-DOPS • Specific targeting—octreotide, desmopression, or erythropoietin Adapted from Mathias et al. (2013).

section 24 Neurological disorders 6158 Individual autonomic disorders Primary autonomic failure The onset is usually slow and insidious in chronic autonomic failure, unlike the acute/subacute dysautonomias. Chronic autonomic failure The most common of these disorders is multiple system atrophy where there is additional neurological disease, unlike pure auto- nomic failure. Patients are usually middle-aged at presentation, although with increasing awareness, it is being diagnosed in younger patients. In pure autonomic failure, diagnosis is usually considered be- cause of orthostatic hypotension. Nocturia (rather than incon- tinence) is frequent, presumably because fluid shifts from the peripheral to the central compartment, elevates blood pressure and improves renal perfusion. Constipation often occurs. In temperate climates, hypohidrosis may not be recognized, unlike tropical areas where heat intolerance and collapse may occur. In men, impotence is common. The clinical and laboratory findings indicate wide- spread sympathetic failure, usually with parasympathetic deficits. Physiological and biochemical tests, along with limited neuropatho- logical data, indicate a peripheral autonomic lesion. Management is directed predominantly towards reducing orthostatic hypotension. Although recovery does not occur, the overall prognosis in pure autonomic failure is good. Multiple system atrophy is a nonfamilial and sporadic disorder with autonomic features and additional neurological (parkinsonian, cerebellar, and pyramidal) features (see Box 24.14.7) that occur at any stage and in any combination, in an unpredictable manner. Thus, patients may initially consult a range of specialists. It is ran- domly progressive, which adds to difficulty in diagnosis. It is syn- onymous with Shy–Drager syndrome, the former name. In multiple system atrophy, the additional neurological fea- tures are predominantly parkinsonian; in a smaller number they are cerebellar and, as the disease advances, there is usually a mix- ture of features (Fig. 24.14.7). The neuropathological findings include striatonigral degeneration in multiple system atrophy (parkinsonian) and olivopontocerebellar degeneration in multiple system atrophy (cerebellar), with both changes often seen in ei- ther form. There is cell loss in various brain-stem nuclei (including the vagal nuclei), in the intermediolateral cell mass in the thoracic and lumbar spinal cord, and in Onuf’s nucleus in the sacral spinal cord, which accounts for the various autonomic and allied abnor- malities. The paravertebral ganglia and visceral (enteric) plexus are spared. A specific feature is the presence of intracytoplasmic, argyrophilic, oligodendrocyte inclusion bodies, within the brain and spinal cord. Many patients with multiple system atrophy have parkinsonian features and distinguishing multiple system atrophy
Table 24.14.3 Drugs used in the treatment of orthostatic hypotension Site of action Drugs Predominant action Plasma volume: expansion Fludrocortisone Mineralocorticoid effects—increased plasma volume Sensitization of α-adrenoreceptors Kidney: reducing diuresis Desmopressin Vasopressin2-receptors on renal tubules Vessels: vasoconstriction (adrenoceptor mediated) Ephedrine Indirectly acting sympathomimetic Resistance vessels Midodrine,a phenylephrine, methylphenidate Directly acting sympathomimetics Tyramine Release of noradrenaline Clonidine Postsynaptic α2-adrenoceptor agonist Yohimibine Presynaptic α2-adrenoceptor antagonist DL-DOPS and L-DOPS Prodrug resulting in formation of noradrenaline Capacitance vessels Dihydroergotamine Direct action on α-adrenoceptors Vessels: vasoconstriction (nonadrenoceptor mediated) Triglycyl-lysine-vasopressin (glypressin) Vasopressin1-receptors on blood vessels Vessels: prevention of vasodilatation Propranolol Blockade of β2-adrenoceptors Indomethacin Prevents prostaglandin synthesis Metoclopramide Blockade of dopamine receptors Vessels: prevention of postprandial hypotension Caffeine Blockade of adenosine receptors Octreotide Inhibits release of vasodilator gut/pancreatic peptides Acarbose, voglibose Intestinal α-glucosidase inhibitors Enhancing sympathetic ganglionic transmission Pyridostigmine Acetylcholine esterase inhibition Heart: stimulation action Pindolol, xamoterol Intrinsic sympathomimetic Red cell

mass: increase Erythropoietin Stimulates red cell production a Through its active metabolite. Adapted from Mathias CJ, Iodice V, Low DA, Bannister R (2013). Clinical features and evaluation of the primary chronic autonomic failure syndromes. In: Mathias CJ, Bannister R (eds) A Textbook of Clinical Disorders of the Autonomic Nervous System, 5th edition. Oxford University Press, Oxford.

24.14 Diseases of the autonomic nervous system 6159 from idiopathic Parkinson's disease, especially in the early stages, is difficult. Thus, the true prevalence and incidence of multiple system atrophy are not known. At post-mortem examination, up to a quarter of patients previously considered to have Parkinson's disease have the characteristic neuropathological features of multiple system atrophy. In multiple system atrophy (parkinsonian), bradykinesia and rigidity are often bilateral, with minimal or no tremor, unlike Parkinson's disease; however, this may not be a useful discrimin- ator in an individual. Lack of a motor response to l-dopa is not indicative of multiple system atrophy, because two-thirds respond initially, although refractoriness and side effects eventually reduce the benefit. The presence of autonomic failure (especially ortho- static hypotension) and unexplained genitourinary symptoms with sphincter disturbance should alert one to the possibility of mul- tiple system atrophy in patients with parkinsonian or cerebellar signs. Oropharyngeal dysphagia and respiratory abnormalities fa- vour multiple system atrophy, although these often occur later. The combination of cardiovascular autonomic failure and an abnormal urethral/anal sphincter electromyogram, with characteristic clin- ical features, are virtually confirmatory of multiple system atrophy. Additional evaluation includes neuroimaging studies using MRI, positron emission tomography, and proton magnetic resonance spectroscopy of the basal ganglia, which are abnormal, at least in established cases. Clonidine growth hormone testing, based on α2-adrenoceptor stimulation of the hypothalamus with release of human growth hormone-releasing factor, distinguishes central from peripheral autonomic failure and separates Parkinson's dis- ease from multiple system atrophy (Fig. 24.14.8); whether this is the case in the early stages of parkinsonism and in patients on dopaminergic agents (which are growth hormone secretagogues) remains to be resolved. The prognosis in multiple system atrophy is poor compared with idiopathic Parkinson's disease and pure autonomic failure. Akinesia and rigidity often worsen, with increasing refractoriness and side effects (including orthostatic hypotension) from antiparkinsonian therapy. As the disease advances there is often considerable immo- bility and difficulty in communication. In multiple system atrophy (cerebellar), worsening truncal ataxia causes falls and an inability to stand upright; orthostatic hypotension compounds the disabilities. Box 24.14.7 Investigations in autonomic failure Cardiovascular Physiological • Head-up tilt, standing; Valsalva manoeuvre • Pressor stimuli: isometric exercise, cutaneous cold, mental arithmetic • Heart rate responses: deep breathing, hyperventilation, standing, head-up tilt • Liquid meal challenge • Exercise testing • Carotid sinus massage • Situational orthostasis—cervical and head movements, arm movements • 24-h ambulatory blood pressure and heart rate monitoring using the autonomic protocol Biochemical • Basal plasma noradrenaline, adrenaline, and dopamine levels • Plasma noradrenaline: supine and standing • Urinary catecholamines Pharmacological • Noradrenaline—α-adrenoceptors, vascular • Isoprenaline—β-adrenoceptors, vascular and cardiac • Tyramine—pressor and noradrenaline response • Edrophonium—noradrenaline response • Clonidine—stimulation (for growth hormone response) and suppres- sion (of plasma noradrenaline and adrenaline) • Atropine—heart rate response Sweating • Thermoregulatory: increase core temperature by 1 °C • Sweat gland response to intradermal acetylcholine • Sympathetic skin response Gastrointestinal • Barium studies, videocinefluoroscopy, endoscopy, gastric-emptying studies, anal sphincter electromyography Renal

function and urinary tract • Day and night urine volumes and sodium/potassium excretion • Urodynamic studies, intravenous urography, ultrasound examination, urethral sphincter electromyography Sexual function • Penile plethysmography • Intracavernosal papaverine • Ultrasound examination Respiratory • Laryngoscopy • Sleep studies to assess apnoea/oxygen desaturation Eye • Lacrimal function: Schirmer's test • Pupillary function: pharmacological and physiological From Mathias and Bannister (2013). P C M PAF PD PD+AF PSP LBD Autonomic Parkinsonian Cerebellar/ Pyramidal Dementia MSA Fig. 24.14.7 The major clinical features in parkinsonian syndromes and in allied disorders with autonomic failure. These include the three major neurological forms of multiple system atrophy—the parkinsonian form (MSA-P, also called striatonigral degeneration), the cerebellar form (MSA- C, also called olivopontocerebellar atrophy), and the multiple or mixed form (MSA-M, which has features of both other forms)—pure autonomic failure (PAF), idiopathic Parkinson's disease (IPD), Parkinson's disease with autonomic failure (PD + AF), progressive supranuclear palsy (PSP), and diffuse Lewy body disease (LBD). Adapted from Bannister R, Iodice V, Vichayanrat E, Mathias CJ (2013). Clinical features and evaluation of the primary chronic autonomic failure syndromes. In: Mathias CJ, Bannister R (eds) A Textbook of Clinical Disorders of the Autonomic Nervous System, 5th edition. Oxford University Press, Oxford, and Iodice V, Low DA,
Vichayanrat E, Mathias CJ (2012). Cardiovascular autonomic dysfunction in Parkinson's disease and parkinsonian syndromes. In: Ebadi M, Pfeiffer RF, Wszolek ZK (eds) Parkinson's Disease, 3rd edition. CRC Press, Florida.

section 24 Neurological disorders 6160 Incoordination of the upper limbs, speech defects, and nystagmus result in further disabilities. Respiratory complications include obstructive apnoea (caused by laryngeal abductor cord paresis), and central apnoea may necessi- tate tracheostomy. Oropharyngeal dysphagia enhances the risk of aspiration, especially when vocal fold paresis is present; a percutan- eous feeding gastrostomy may be needed. Urinary bladder dysfunc- tion is distressing, and its management, together with management of constipation and, if appropriate, treatment of sexual dysfunc- tion is important in improving quality of life. There is often a need for specialist therapists, including speech and language therapists, physiotherapists, dietitians, and occupational therapists. As the neurological decline is inexorable, supportive therapy is crucial in management of multiple system atrophy, and should incorporate the family, carers, and community along with the primary care medical practitioner and therapists. Orthostatic hypotension and other features of autonomic failure appear more common in Parkinson's disease than previously thought. A current hypothesis places nonmotor lesions in the ol- factory and brain-stem areas, including vagal nuclei, before onset of parkinsonian features. In Parkinson's disease the autonomic lesions appear peripheral and thus similar to pure autonomic failure. This is based on low basal plasma noradrenaline levels, and radionuclide and positron emission tomography studies, which indicate cardiac postganglionic sympathetic denervation. This is distinct from mul-tiple system atrophy where the lesions are preganglionic. Orthostatic hypotension and autonomic failure may precede the motor and cog- nitive decline in diffuse Lewy body disease.
Acute/subacute dysautonomias These disorders are relatively rare and consist of three main var-ieties: pure pandysautonomia (with features of both sympathetic and parasympathetic failure); pandysautonomia with additional neuro- logical features usually indicative of a peripheral neuropathy; and pure cholinergic dysautonomia. The prognosis in pandysautonomias is variable, with substantial recovery in some. Recovery after im- munoglobulin therapy favours an immunological basis, and the pos- sibility of a Guillain–Barré syndrome variant. In pure cholinergic

dysautonomia, described mainly in children and young adults, there is widespread parasympathetic failure with blurred vision, dry eyes, xerostomia, dysphagia with middle and lower oesophagus involve- ment, severe constipation, and urinary retention. Clinical findings include dilated pupils, an elevated heart rate, dry and warm skin, a distended abdomen, and a palpable urinary bladder. Anhidrosis may result in hyperthermia. The term ‘cholinergic’ is used because both parasympathetic and cholinergic sympathetic pathways (to sweat glands) are affected. Sympathetic vasoconstrictor function is preserved and orthostatic hypotension does not occur. Recovery is poor, but the prognosis is good if the condition is de- tected early. Management includes supportive therapy and adequate fluid and nutrient replacement of losses due to gastrointestinal and sudomotor failure. Barium studies should be avoided because contrast medium accumulates in the atonic colon. The differential diagnosis includes exposure to drugs, poisons, and toxins with anti- cholinergic effects. Similar autonomic features occur in thorn apple (Datura stramonium) seed poisoning; the poisoning is associated with hallucinations, hyperreflexia, and clonic jerking movements, and recovery occurs in a few days. Botulism B affects cholinergic systems but spares motor systems, and substantial recovery is ex- pected within 3 months of exposure. Secondary disorders Many disorders are associated with autonomic failure; a few are described here. Riley–Day syndrome (familial dysautonomia) This is a recessive genetic defect characterized by absent lingual fungiform papillae, lack of corneal reflexes, absence of overflow emotional tears, decreased deep tendon reflexes, and a diminished response to pain and temperature; the disease occurs typically in children of Ashkenazi Jewish extraction. An abnormal intradermal histamine skin test (absent axon flare) and pupillary hypersensitivity to cholinomimetics provide diagnostic confirmation. Prenatal diag- nosis is possible with the genetic markers linked to chromosome 9 (b) 6 Growth hormone (mU/l) 22 20 18 16 14 Time (min) 12 10 8 4 2 0 12 11 10 9 8 7 6 5 4 3 2 1 0 Growth hormone (mU/l) −10 15 30 45 60 0 –10 15 30 45 60 0 Time (min) IPD (n = 14) MSA-C (n = 16) Parkinsonian MSA (n = 15) Controls (n = 27) PAF (n = 19) MSA (n = 31) (a) Fig. 24.14.8 (a) Serum growth hormone (GH) concentrations before (0) and at 15-min intervals for 60 min after clonidine (2 μg/kg per min) in normal individuals (controls), and in patients with pure autonomic failure (PAF) and multiple system atrophy (MSA). GH concentrations rise in controls and in patients with PAF with a peripheral lesion; there is no rise in patients with MSA with a central lesion. (b) Lack of serum GH response to clonidine in MSA (the cerebellar form and the parkinsonian forms) in contrast to patients with idiopathic Parkinson’s disease with no autonomic deficit (IPD), in whom there is a significant rise in GH levels. (a) From Thomaides T et al. (1992). The growth hormone response to clonidine in central and peripheral primary autonomic failure. Lancet 340, 263–6. Copyright © 1992, with permission from Elsevier. (b) From Kimber JR, Watson L, Mathias CJ (1997). Distinction of idiopathic Parkinson’s disease from multiple system atrophy by stimulation of growth hormone release with clonidine. Lancet 349, 1877–81. Copyright © 1997, with permission from Elsevier.

 (q31). Autonomic underactivity and overactivity include lability of blood pressure (hypertension and orthostatic hypotension), inter- mittent hyperhidrosis, periodic vomiting, dysphagia, constipation, and diarrhoea. The neurological abnormalities include emotional and behavioural disturbances, and sensory deficits that result in in- jury to skin and joints. Skeletal problems (scoliosis), and respira- tory (aspiration) and renal failure contribute to a poor prognosis. Anticipation of complications and adequate therapy have extended survival into adulthood. Amyloid neuropathy Deposition of amyloid into autonomic nerves can occur in reactive systemic (AA) amyloidosis (in chronic inflammatory disorders) or in

immunoglobulin light chain (AL) amyloidosis (with lymphomas). In familial amyloid polyneuropathy the sensory, motor, and autonomic abnormalities result from deposition in peripheral nerves of mutated variant transthyretin, produced mainly in the liver. Symptoms of a sensory and motor neuropathy often begin in adulthood in the lower limbs in Portuguese, Japanese, and Swedish forms (familial amyloid polyneuropathy I), and in the upper limbs in Indian/Swiss and German/Maryland forms (familial amyloid polyneuropathy II). These and other forms are now classified by the chemical and molecular nature of abnormal fibrillary protein, immunologically related to transthyretin. The most common is based on the first point mutations in the transthyretin gene associated with familial amyloid polyneuropathy—methionine-30 in the Portuguese form. The cardiovascular, gastrointestinal, and urinary systems are af- fected at variable stages, with the disease progressing relentlessly. Autonomic symptoms and signs may be dissociated, leading to underrecognition of the autonomic deficit. Liver transplantation re- duces variant transthyretin levels and prevents progression of neur- opathy. Its ability to reverse neuropathy is unclear, emphasizing the need for intervention before nerve damage occurs. Dopamine β-hydroxylase deficiency This rare disorder (with 14 patients reported, 2 of whom are siblings) was recognized in the mid-1980s. Enzymatic deficiency probably occurs at birth but presentation is often in childhood. Orthostatic hypotension has been the clue to recognition. The clinical features indicate sympathetic adrenergic failure, with sparing of sympathetic cholinergic and parasympathetic function; thus, sweating is pre- served, and urinary bladder and bowel functions appear normal. In men, erection is possible but ejaculation difficult to achieve. Basal levels of plasma noradrenaline and adrenaline are undetectable but dopamine is abnormally elevated. Sympathetic nerve terminals, ex- cept for the enzymatic and functional defect, are otherwise intact, as demonstrated by electron microscopy, immunohistochemistry, and sympathetic microneurography. Effective treatment is with the prodrug l-dihydroxyphenylserine (l-DOPS), which is given by mouth. It has a structure similar to noradrenaline and is con- verted by the enzyme dopa-decarboxylase (abundantly present in extraneuronal tissue such as liver and kidneys) to noradrenaline, thus bypassing the dopamine β-hydroxylase deficiency and re- placing the deficient neurotransmitter (see Fig. 24.14.2a). L-DOPS has been successfully used in such patients and has transformed their lives. It has also been used successfully in orthostatic hyper- tension due to pure autonomic failure, multiple system atrophy, and Parkinson’s disease. Diabetes mellitus In patients with long-standing diabetes, especially those on insulin, there is a high incidence of peripheral and autonomic neuropathy. Vagal denervation occurs earlier, impairing heart rate variability. Reduced sympathetic activity (e.g. in the feet), may increase blood flow substantially at an early stage before detection of neuropathy. Orthostatic hypotension may be enhanced by insulin. There may be sweating abnormalities (gustatory sweating), delayed stomach emptying (gastroparesis diabeticorum), impaired urinary bladder function (diabetic cystopathy), and impotence. Diarrhoea may be extremely distressing. Spinal cord injuries Autonomic dysfunction affecting many systems occurs in spinal injuries, depending on the lesion level and the degree of complete- ness. Cardiovascular dysfunction may be life-threatening, espe- cially in high lesions in the acute phase of spinal shock, because lack of sympathetic activity with increased vagal tone may cause bradycardia and cardiac arrest (Fig. 24.14.9). After a few weeks, spinal shock passes and isolated spinal reflex activity returns; in cervical and high thoracic lesions, abnormal spinal activation re- sults in the syndrome of autonomic dysreflexia. This is induced by cutaneous, skeletal muscle, or visceral stimuli (not necessarily nox- ious) below the level of the lesion. Thus, severe muscle spasms, an anal fissure, or a blocked urethral catheter can result in paroxysmal hypertension (due to increased spinal sympathetic nerve activity, independent of normal cerebral pathways) with

associated brady- cardia (because of preserved baroreceptor afferents and vagal ef- ferent pathways—Fig. 24.14.10). Patients with lesions below T6 are typically spared. Patients with high lesions are also prone to ortho- static hypotension, which compounds difficulties in management, especially shortly after injury. Drugs Dysfunction may result from an autonomic neuropathy (as in- duced by alcohol, vincristine, and perhexiline maleate) or through pharmacological effects. The latter may be expected with the sym- patholytic agents, or may be a minor unexpected effect in suscep- tible individuals. An example is the anticholinergic bladder effects of disopyramide, which may cause urinary retention in patients with prostatic hyperplasia. A variety of toxins and poisons, including mushroom toxicity and botulism, as well as nerve gases such as sarin, affect the autonomic nervous system. The first-dose effect of angiotensin-converting enzyme inhibitors and prazosin may be mediated by the Jarisch–Bezold reflex. Autonomic overactivity may occur during withdrawal of clonidine, alcohol, and opiates. Intermittent autonomic dysfunction There is usually no damage to autonomic nerves and autonomic dys- function is often short-lived. Autonomic (neurally) mediated syncope Syncope (fainting, loss of consciousness) may result from an inter- mittent and transient abnormality with increased cardiac parasympa- thetic (causing severe bradycardia, cardioinhibition) and/or possibly sympathetic withdrawal (causing hypotensive vasodepression). The episodes may be cardioinhibitory, vasodepressor, or mixed

 (Fig. 24.14.11). There are three major groups: vasovagal syncope, carotid sinus hypersensitivity, and situational syncope. Between epi- sodes, screening autonomic tests usually reveal no abnormalities. The most common disorder is vasovagal syncope. This is often fa- milial and more likely in females; it may present in the early teenage years and is induced by stimuli such as the sight of blood, pain, nee- dles, and at times even discussion of venepuncture. Hypotension is more likely in the upright position and may occur while standing still, especially in warm weather, and with salt and fluid depletion. Testing includes head-up tilt, which sometimes may need to be prolonged for about 45 minutes, or with introduction of a provoca- tive stimulus such as venepuncture, cervical or arm movements, ideally during head-up tilt. A variety of physiological (head-up tilt plus lower body negative pressure) or pharmacological (isopren- aline infusions or glyceryl trinitrate) stimuli have been used to un- mask an episode, but may result in false-positive results. Cardiac conduction disorders and other causes of syncope (neurological or metabolic) should be excluded. Treatment includes reducing or preventing exposure to precipitating causes and behavioural psy- chotherapy in patients with phobias. Added salt, fluid repletion, and physical conditioning are often useful. Techniques to increase sympathetic activity and maintain or raise blood pressure (such as sustained hand grip) and to prevent pooling (calf muscle activation) are helpful, especially in patients who have a warning window of symptoms before syncope. Sitting down, or lying flat, with the legs raised should prevent most episodes. Drugs such as fludrocortisone and vasopressor agents (ephedrine and midodrine) can be benefi- cial. Antidepressants such as the serotonin selective reuptake inhibi- tors (SSRIs) have been used with equivocal results. β-Adrenergic blockers provide no benefit for younger patients in most cases. The long-term prognosis is favourable. In older people, carotid sinus hypersensitivity is increasingly rec- ognized, especially in those with falls of otherwise unknown cause (Fig. 24.14.12). A classic history of syncope induced by head move- ments or collar tightening may be provided, although in many the precipitating factors are unclear. Carotid sinus massage should be performed in the laboratory with the requisite precautions, ideally using continuous blood pressure and heart rate recordings, with the patient also tilted head up, because hypotension is more likely to occur when sympathetic activation is needed. Treatment, especially of the cardioinhibitory forms, includes a

cardiac demand pace- maker; vasodepressor forms may require pressor agents. Surgical denervation of the carotid sinus has been used successfully, espe- cially where unilateral hypersensitivity occurs. A variety of other stimuli, acting through short-lived autonomic mechanisms, can also cause syncope, considered under situational BP (mmHg) HR (beats/min) Plasma NA and A (ng/ml) Time (min) IVP (mmHg) 200 0 100 0 100 0 0.20 0.00 Bladder stimulation Fig. 24.14.10 Blood pressure (BP), heart rate (HR), intravesical pressure (IVP), and plasma noradrenaline (NA) and adrenaline (A) concentrations in a tetraplegic patient before, during, and after bladder stimulation induced by suprapubic percussion of the anterior abdominal wall. The rise in BP is accompanied by a fall in heart rate as a result of increased vagal activity in response to the rise in blood pressure. The level of plasma noradrenaline (open histograms), but not adrenaline (filled histograms), rises, suggesting an increase in sympathetic neural activity independent of adrenomedullary activation. From Mathias CJ, Frankel HL (1986). The neurological and hormonal control of blood vessels and heart in spinal man. J Autonom Nervous Syst Suppl, 457–64. (a) BP (mm Hg) Time (min) HR (beats/min) 200 0 100 6 h post atropine (0.6 mg IV) Off respirator Atropine 0.6 mg IV (b) 20 min post atropine (0.6 mg IV) Off respirator for suction 0 Time (min) BP (mm Hg) HR (beats/min) 200 0 0 100 Fig. 24.14.9 (a) The effect of disconnecting the respirator (as required for aspirating the airways) on the blood pressure (BP) and heart rate (HR) of a recently injured tetraplegic patient (C4–5 lesion) in spinal shock, 6 h after the last dose of intravenous atropine. Sinus bradycardia and cardiac arrest (also observed on the electrocardiogram) were reversed by reconnection, intravenous atropine, and external cardiac massage. (b) The effect of tracheal suction 20 min after atropine. Disconnection from the respirator and tracheal suction did not lower either heart rate or blood pressure. (a) From Frankel HL, Mathias CJ, Spalding JMK (1975). Mechanisms of reflex cardiac arrest in tetraplegic patients. Lancet 2, 1183–5. Copyright © 1975, with permission from Elsevier. (b) From Mathias CJ (1976). Bradycardia and cardiac arrest during tracheal suction—mechanisms in tetraplegic patients. European Journal of Intensive Care Medicine 2, 147–56. Copyright © 1976, Springer-Verlag, with permission of Springer.

24.14 Diseases of the autonomic nervous system 6163 0 140 0 160 VENEPUNCTURE Blood pressure (a) (b) (c) mm Hg Heart rate bpm 60° HEAD-UP TILT Blood pressure mm Hg 60° HEAD-UP TILT START OF PRE-SYNCOPAL SYMPTOMS 0 140 0 160 Heart rate bpm 0 120 0 110 Heart rate bpm Blood pressure mm Hg 60° HEAD-UP TILT Fig. 24.14.11 Blood pressure and heart rate with continuous recordings in (a) a patient with the mixed (cardioinhibitory and vasodepressor) form of vasovagal syncope. (b) in a patient with the predominantly vasodepressor form of vasovagal syncope. (c) in a patient with the cardioinhibitory form of vasovagal syncope. In: Jameson JL, De Groot LJ (eds) (2015). Endocrinology, 7th edition, Elsevier, Philadelphia, PA. Copyright © 2016, with permission from Elsevier.

section 24 Neurological disorders 6164 syncope. This may be together with factors such as heat or drugs that cause vasodilatation or reduce intravascular volume, thus increasing the tendency to hypotension and syncope. Examples include syn- cope associated with glossopharyngeal neuralgia (caused by swal- lowing), or induced by micturition, defecation, coughing, laughing, and playing wind instruments. Postural tachycardia syndrome Postural tachycardia syndrome is a poorly understood but important cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction. The onset might be linked to infection, trauma, surgery, or stress. Symptoms, which usually occur when standing and can be exacerbated by common stimuli in daily life, including modest exertion, food ingestion, heat, and time of day (morning), and appear to disrupt lives

almost disproportionately. There is a substantial rise in heart rate (over 30 beats/min or to 120 beats/min or higher) without orthostatic hypotension, hence the term ‘postural (orthostatic) tachycardia syndrome’, or pos- tural tachycardia syndrome (Fig. 24.14.13). Syncope may occur. Cognitive dysfunction can occur. Proposed pathophysiological Left carotid sinus hypersensitivity Blood pressure mm Hg Heart rate bpm 160 0 LEFT CAROTID SINUS MASSAGE 120 0 Fig. 24.14.12 Continuous blood pressure and heart rate measured noninvasively in a patient with falls of unknown aetiology. Left carotid sinus massage caused a fall in both heart rate and blood pressure. The findings indicate the mixed (cardioinhibitory and vasodepressor) form of carotid sinus hypersensitivity. 0 200 0 140 0 200 0 140 10 MIN OF 60° HEAD UP TILT 10 MIN OF 60° HEAD UP TILT PoTS Normal Heart rate bpm Blood pressure mm Hg Heart rate bpm Blood pressure mm Hg Fig. 24.14.13 Blood pressure and heart rate measured continuously before, during, and after 60° head-up tilt in a normal person (upper panel), and in a patient with the postural tachycardia syndrome (PoTS) (lower panel). Adapted from Mathias et al. (2012).

24.14 Diseases of the autonomic nervous system 6165 mechanisms include alterations in neural control, humoral factors, vascular properties, and intravascular volume, as well as physical deconditioning. Associated disorders include a partial autonomic neuropathy, chronic fatigue syndrome, mitral valve prolapse, mast cell activation disorder, and hyperventilation. A rare gen- etic noradrenaline transporter deficit, or drugs, may be causative. A common association is with some of the classifications of Ehlers- Danlos syndromes, e.g., Hypermobile EDS (type 3 hEDS). The rela- tionship of postural tachycardia syndrome to previously considered psychosomatic disorders, such as soldier’s heart or da Costa’s syn- drome, remains unclear. Investigation should include evaluating potential causes and asso- ciated factors, which is an integral part of determining the patho- physiological processes involved to aid management. A multifactorial and individualized treatment strategy that includes pharmacological agents as well as nonpharmacological measures and interventions is often required. Other factors, including underlying and associated disorders, are also essential to consider. Nonpharmacological meas- ures include those as used in autonomic mediated syncope, such as salt and fluid repletion and graded exercise. In those with a low supine blood pressure, drugs to raise blood pressure may be used. These may include fludrocortisone, ideally in low doses to avoid adverse effects, such as a low plasma potassium level. It should not be used in patients with a tendency to retain fluid. A vasoconstrictor such as midodrine is often of value. Vasoconstrictors that increase heart rate, such as ephedrine, must be avoided. Cardioselective β-adrenergic blockers have a role, but not when the tachycardia is in response to vascular pooling when upright. The selective sinus node blocker, ivabradine, may have a role in reducing tachycardia. In patients with postural tachycardia syndrome who have a normal or elevated supine blood pressure, fludrocortisone and midodrine should not be used. In patients who experience marked postprandial features, especially those in whom other treat- ments have been ineffective, subcutaneous octreotide can be bene- ficial in small doses. SSRIs have been used with mixed results. With appropriate management, the prognosis of postural tachycardia syn- drome is favourable. Spontaneous recovery may occur in some. Initial orthostatic hypotension Initial orthostatic hypotension is defined as a transient fall in blood pressure (>40 and >20 mm Hg systolic and diastolic, respectively) within 15 s after standing, accompanied by symptoms of cerebral hypoperfusion. This phenomenon is separated from orthostatic hypotension by its short duration—between 20 and 30 s—and a subsequent recovery of blood pressure to preorthostatic levels; it may cause a variety of posturally induced symptoms and even syncope or presyncope. The pathophysiological mechanisms in- clude a mismatch between cardiac output and vascular resistance resulting from an impaired calf muscle pump, rapid vasodilation, or activation of

cardiopulmonary mechanoreceptors in response to increasing right atrial pressure leading to sudden sympathetic neural withdrawal. Management should include advice on non-pharmacological measures, including techniques to enhance sym- pathetic activity to raise blood pressure and prevent pooling, such as the use of isometric hand exercise, leg crossing, and tensing of lower limb muscles prior to and during the assumption of the up- right posture (Fig. 24.14.4). Primary or essential hyperhidrosis Excessive sweating without an underlying cause (such as hyperthy- roidism, infection, etc.) may be familial or sporadic, and it may be lo- calized, involving areas such as the palms, axillae, soles of the feet, or the face. In some there is widespread sweating. It can be distressing and socially destructive. Factors that provoke sweating include stress, heat, and exercise. In primary hyperhidrosis, investigation reveals no underlying pathology or autonomic deficit. Treatment options include percutaneous surgical sympathectomy for upper limb and facial sweating; in some, after surgery a complication is compensatory hyperhidrosis in the innervated areas, which some find worse than the original problem; treatment is with low doses of clonidine and anticholinergics (such as probanthine), iontophor- esis for palmar and plantar sweating, and botulinum toxin injections for localized areas. Cognitive behavioural therapy and anxiolytics, including SSRIs, have a role. FURTHER READING Low PA, Bennarroch EE (eds) (2008). Clinical autonomic disorders, 3rd edition. Lippincott Williams & Wilkins, Baltimore, MD. Mathias CJ (2009). Autonomic dysfunction. In: Clarke C, et al. Neurology: a queen square textbook. pp. 871–982. Wiley-Blackwell, Oxford. Mathias CJ, Bannister R (2013). Autonomic failure: a textbook of clinical disorders of the autonomic nervous system, 5th edition. Oxford University Press, Oxford. Mathias CJ, et al. (2012). Postural tachycardia syndrome—current experience and concepts. Nat Rev Neurol, 8, 22–34. Mathias CJ, et al. (2013). Autonomic dysfunction: recognition, diagno sis, investigation, management, and autonomic neurorehabilitation. Handb Clin Neurol, 110, 239–53. Robertson D, et al. (2012). Primer on the autonomic nervous system, 3rd edition. Elsevier, Waltham, MA.

Revision #1
Created 2026-01-22 16:43:23 UTC by Omar Ayman
Updated 2026-01-22 16:43:23 UTC by Omar Ayman