Fundamentals in CLINICAL NEUROLOGY

2nd Edition

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JAYPEE

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Section 3: Major Categories of Neurologic Disease

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CHAPTER

19 Disorders of Autonomic Nervous System

INTRODUCTION

- Autonomic nervous system (ANS) is a control system that acts largely unconsciously and regulates bodily functions such as the heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. This system is the primary mechanism in control of the *fight-or-flight response*.
- Disorders of ANS are the collection of syndromes and diseases affecting the autonomic neurons, either parasympathetic or sympathetic, or both, which can be hereditary or acquired in nature.

DIVISIONS OF AUTONOMIC NERVOUS SYSTEM

- Parasympathetic nervous system
- Sympathetic nervous system

Physiology of Autonomic Nervous System (Fig. 19.1)

- The activity of ANS is regulated by central neurons which post integration of afferent information adjust the autonomic outflow as per the need.

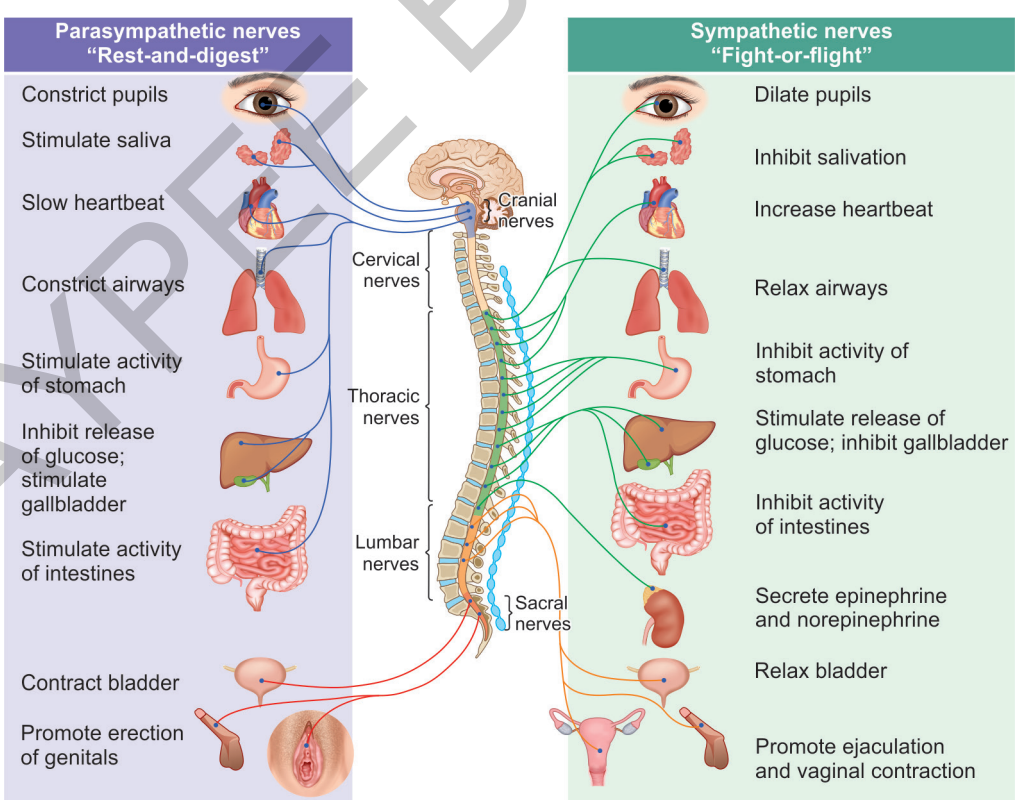


FIG. 19.1: Physiology of ANS.
(ANS: autonomic nervous system)

- The preganglionic neurons of the parasympathetic nervous system leave central nervous system (CNS) in the third, seventh, ninth, and tenth cranial nerves as well as the second and third sacral nerves.
- The preganglionic neurons of the sympathetic nervous system exit the spinal cord between the first thoracic and the second lumbar segments.
- The preganglionic fibers are thinly myelinated.
- The postganglionic neurons, located in ganglia outside the CNS, give rise to the postganglionic unmyelinated autonomic nerves that innervate organs and tissues throughout the body **(Fig. 19.2)**.
- Acetylcholine (ACh) is the preganglionic neurotransmitter for both divisions of the ANS as well as the postganglionic neurotransmitter of the parasympathetic neurons.
- Norepinephrine (NE) is the neurotransmitter of the postganglionic sympathetic neurons, except for cholinergic neurons innervating the eccrine sweat glands.
- Purinergic fibers may play a role in the control of vasomotor tone and in the regulation of regional blood flow.
- Responses to sympathetic and parasympathetic stimulation are frequently antagonistic reflecting highly coordinated interactions within the CNS.
- Difference between sympathetic and parasympathetic nervous system is described in **Table 19.1**.

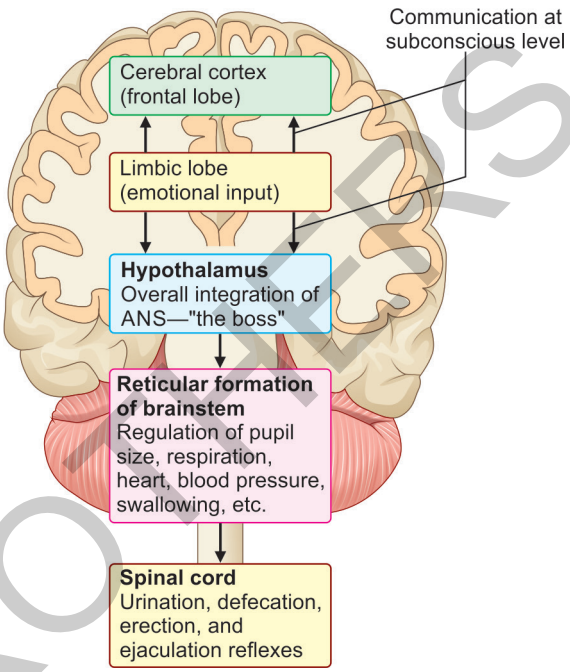


FIG. 19.2: Central control of the ANS.
(ANS: autonomic nervous system)

TABLE 19.1: Difference between sympathetic and parasympathetic nervous system.

Sympathetic nervous system (fight-or-flight)	Parasympathetic nervous (rest-and-digest)
Diverts blood flow away from the gastrointestinal (GI) tract and skin via vasoconstriction	Dilate blood vessels leading to the GI tract, increasing blood flow
Blood flow to skeletal muscles and the lungs is enhanced (by as much as 1200% in the case of skeletal muscles). Dilates bronchioles of the lung, which allows for greater alveolar oxygen exchange	Constrict the bronchiolar diameter when the need for oxygen has diminished
Increases heart rate and the contractility of cardiac cells (myocytes), thereby providing a mechanism for enhanced blood flow to skeletal muscles. Provides vasodilation for the coronary vessels of the heart	Dedicated cardiac branches of the vagus and thoracic spinal accessory nerves impart parasympathetic control of the heart
Dilates pupils and relaxes the ciliary muscle to the lens, allowing more light to enter the eye and far vision	During accommodation, causes constriction of the pupil and contraction of the ciliary muscle to the lens, allowing for closer vision
Constricts all the intestinal sphincters and the urinary sphincter	Stimulates salivary gland secretion, and accelerates peristalsis, mediating digestion of food and, indirectly, the absorption of nutrients
Inhibits peristalsis	The PNS is also involved in the erection of genital tissues via the pelvic splanchnic nerves 2–4
Stimulates orgasm	The PNS is responsible for stimulating sexual arousal

(PNS: peripheral nervous system)

CENTRAL CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

- *Amygdala*: This is the main limbic region for emotions:
  - Stimulates sympathetic activity, especially previously learned fear-related behavior
  - Can be voluntary when decide to recall frightful experience—cerebral cortex acts through amygdala
  - Some people can regulate some autonomic activities by gaining extraordinary control over their emotions.
- *Hypothalamus*: Main integration center
- *Reticular formation*: Most direct influence over autonomic function

CAUSES OF AUTONOMIC NERVOUS SYSTEM DISORDERS

Autonomic disorders may result from disorders that damage autonomic nerves or parts of the brain that help control body processes, or they may occur on their own, without a clear cause.

- *Common causes of autonomic disorders are*:
  - Diabetes (the most common cause)
  - Peripheral nerve disorders
  - Aging
  - Parkinson disease
- *Other, less common causes include the following*:
  - Autonomic neuropathies
  - Multiple system atrophy (MSA)
  - Pure autonomic failure
  - Spinal cord disorders
  - Certain drugs
  - Disorders of the neuromuscular junction (where nerves connect with muscles), such as botulism and Lambert–Eaton syndrome
  - Certain viral infections
  - Injury to nerves in the neck, including that due to surgery

CLASSIFICATION OF AUTONOMIC NERVOUS SYSTEM DISORDERS

Diseases Affecting Central Nervous System

- Progressive autonomic failure (PAF) [idiopathic orthostatic hypotension (IOH)]
- Pure PAF
- PAF with parkinsonian features (PAF-P)
- PAF with MSA (Shy–Drager syndrome) (PAF-MSA)
- Cerebrovascular disease
- Brainstem tumors
- Multiple sclerosis
- Adie's syndrome
- Tabes dorsalis

Diseases Affecting the Peripheral Autonomic Nervous System

- Disorders with no associated peripheral neuropathy
- Acute and subacute autonomic neuropathy
- Pandysautonomia
- Cholinergic dysautonomia
- Botulism
- Disorders associated with peripheral neuropathy
- Autonomic dysfunction clinically important
- Diabetes
- Amyloidosis
- Acute inflammatory neuropathy
- Acute intermittent porphyria
- Familial dysautonomia (Riley–Day syndrome)
- Chronic sensory and autonomic neuropathy

CLINICAL FEATURES OF AUTONOMIC NERVOUS SYSTEM DISORDERS

- Clinical features of autonomic disorders cover a wide spectrum and result from underactivity or overactivity.
  - Sympathetic adrenergic failure causes orthostatic (postural) hypotension and ejaculatory failure in the male
  - Sympathetic cholinergic failure causes anhidrosis
  - Parasympathetic failure causes dilated pupils, fixed heart rate, sluggish urinary bladder, atonic large bowel, and, in the male, erectile failure **(Table 19.2)**.
- In some disorders, particularly in neurally mediated syncope, there may be a combination of overactivity and underactivity, with bradycardia caused by increased parasympathetic activity and hypotension brought about by withdrawal of sympathetic activity.

Cardiovascular System

- *Orthostatic or postural hypotension*:
  - Defined as a fall in blood pressure (BP) of 20 mm Hg systolic or 10 mm Hg diastolic on sitting, standing or during 60° head-up tilt.
- In neurogenic orthostatic hypotension (NOH), levels of plasma noradrenaline do not rise when upright, as occurs in normal subjects.
- Hypoperfusion of organs, especially above heart level such as the brain, causes the malaise, nausea, dizziness,

TABLE 19.2: Common clinical features of ANS disorders.

• *Cardiovascular*:		
	Postural hypotension	Supine hypertension
	Lability of blood pressure	Paroxysmal hypertension
	Tachycardia	Bradycardia
• *Sudomotor*:		
	Hypohidrosis or anhidrotic	Hyperhidrosis
	Gustatory sweating	
	Hyperpyrexia	Heat intolerance
• *Alimentary*:		
	Xerostomia	Dysphagia
	Gastric stasis	Dumping syndromes
	Constipation	Diarrhea
• *Urinary*:		
	Nocturia	Frequency
	Urgency	incontinence
	Retention	
• *Sexual*:		
	Erectile failure	Ejaculatory failure
	Retrograde ejaculation	
• *Eye*:		
	Pupillary abnormalities	Ptosis
	Alacrima	Abnormal lacrimation with food ingestion (gustolacrimal reflex)

TABLE 19.3: Symptoms of hypoperfusion of organs.

Cerebral hypoperfusion	Muscle hypoperfusion	Renal hypoperfusion
• Dizziness • Visual disturbances • Blurred—tunnel • Scotoma • Graying out—blacking out • Color defects • Syncope • Cognitive deficits	• Paracervical and suboccipital ("coat-hanger") ache • Lower back/buttock ache • Subclavian steal-like syndrome • Spinal cord hypoperfusion	• Oliguria

and visual disturbances that often precede loss of consciousness **(Table 19.3)**.

- A variety of symptoms result from hypoperfusion elsewhere.
- Neck pain in a coat-hanger distribution (suboccipital and shoulder regions) differs from other types of neck pain by developing when upright. It is relieved by sitting or lying flat.

- *Nonspecific*:
  - Weakness, lethargy, and fatigue
  - Fall
  - Syncope without orthostatic hypotension (OH)
  - Syncope has many causes (autonomic, cardiac, neurogenic, and metabolic)
  - Autonomic causes of syncope without OH include neurally mediated syncope, where there are transient hypotension and bradycardia.
  - There are three major forms—(1) vasovagal syncope, (2) carotid sinus hypersensitivity, and (3) situational syncope.
  - Blood pressure falls because of sympathetic withdrawal, while heart rate falls because of increased vagal activity.
- *Orthostatic intolerance with posturally induced tachycardia*:
  - When orthostatic intolerance occurs without OH, but with a substantial rise in heart rate (of over 30 beats/min), the term "postural tachycardia syndrome" (PoTS) is used.
  - It predominantly affects women below the age of 50 years.
  - Symptoms include marked dizziness on postural change or modest exertion; syncope may occur.
- *Hypertension*:
  - Unlike hypotension, hypertension typically causes few symptoms other than headaches.
  - In high spinal cord lesions, severe paroxysmal hypertension can develop as part of autonomic dysreflexia, when an uninhibited increase in spinal sympathetic activity is caused by contraction of the urinary bladder, irritation of the large bowel, noxious cutaneous stimulation, or skeletal muscle spasms.
  - In tetanus, hypertension in ventilated patients may be precipitated by muscle spasms or tracheal suction.
  - Intermittent hypertension may occur in the Guillain–Barré syndrome, porphyria, posterior fossa tumors, and pheochromocytoma, often without any evident precipitating cause.
  - Hypertension in the supine position may complicate OH in pure autonomic failure (PAF). The mechanisms include impaired baroreflex activity, adrenoceptor super sensitivity, an increase in central blood volume because of a shift from the periphery, and the effects of drugs used to prevent OH.

- *Heart rate disturbances*:
  - Bradycardia, along with hypertension, may occur in cerebral tumors with or without raised intracranial pressure and during autonomic dysreflexia in high spinal cord injuries.
  - In PoTS, tachycardia usually is associated with head-up postural change and exertion.

Sudomotor System

Anhidrosis or hypohidrosis is common in PAF and differences in sweating may first be noticed during exposure to warm temperatures.

Alimentary System

- Reduced salivation and a dry mouth (xerostomia) occur in autonomic disease.
- Constipation is common in PAF.
- Diarrhea also may occur as a result of overflow.
- Diarrhea, especially at night, can be a distressing problem in diabetes mellitus.

Urinary System

- Nocturnal polyuria is a frequent symptom in PAF.
- The causes include restitution of BP sometimes to elevated levels while supine, and redistribution of blood from the peripheral into the central compartment.
- Autonomic disease can cause urinary frequency, urgency, incontinence, or retention.
- Ureteric reflux predisposes to renal damage, especially in the presence of infection.

Sexual Function

- Failure of erection (parasympathetic damage) may cause impotence.
- Retrograde ejaculation may occur, especially if there are urinary sphincter abnormalities.
- Priapism resulting from abnormal spinal reflexes may occur in patients with spinal cord lesions.

Eyes and Lacrimal Glands

- Mild ptosis is part of Horner's syndrome.
- Pupillary abnormalities may occur with autonomic involvement, miosis in Horner's syndrome, and dilated myotonic pupils in Holmes–Adie syndrome. Impaired tear production may occur in PAF.
- Excessive and inappropriate lacrimation occurs in crocodile tears syndrome (gustolacrimal reflex).

Respiratory System

- Involuntary inspiratory sighs, stridor, and snoring of recent onset are more frequent.
- Nocturnal apnea is caused by involvement of brainstem respiratory centers.

Facial and Peripheral Vascular Changes

- Facial pallor with an ashen appearance with fall of pressure in postural hypotension and restoration of color follows promptly on assuming the supine position.
- In longstanding tetraplegia, hypertension during autonomic dysreflexia is often accompanied by flushing and sweating over the face and neck.
- In Harlequin syndrome, there is vasodilatation and anhidrotic on one side of the face caused by sympathetic impairment, with sparing of the pupil.
- Raynaud's phenomenon may be seen in both PAF and MSA, for uncertain reasons.
- In erythromelalgia, there is limb discomfort with vascular changes.

PHYSICAL EXAMINATION

- *Postural BP and heart rate*:
  - In a normally hydrated patient, a sustained (e.g., >1 minute) decrease of ≥20 mm Hg in systolic BP or a decrease of ≥10 mm Hg in diastolic BP with standing indicates OH.
  - Heart rate change with respiration and standing should be noted; absence of physiologic sinus arrhythmia and failure of heart rate to increase with standing indicate autonomic insufficiency.
  - In contrast, patients with postural orthostatic tachycardia syndrome (POTS), a benign disorder, typically have postural tachycardia without hypotension.
- *Eye examination*:
  - Miosis and mild ptosis (Horner syndrome) suggest a sympathetic lesion.
  - A dilated, unreactive pupil (Adie pupil) suggests a parasympathetic lesion.
- *Genitourinary (GU) and rectal reflexes*:
  - Abnormal GU and rectal reflexes may indicate ANS deficits.
  - Testing includes the cremasteric reflex (normally, stroking the upper inner thigh results in retraction of the testes), anal wink reflex (normally, stroking perianal skin results in contraction of the anal sphincter), and bulbocavernosus reflex (normally,

squeezing the glans penis or clitoris results in contraction of the anal sphincter).
    - In practice, the GU and rectal reflexes are rarely tested, because laboratory testing is much more reliable.
- The extent and distribution of the neurological abnormalities provide important clues to underlying central or peripheral autonomic disorders.
- Examination of other systems, as in hepatic disease or diabetes, is necessary along with biochemically diagnosed.

INVESTIGATIONS

- *Cardiovascular*:
    - Pressor stimuli (isometric exercise, cold pressor, and mental arithmetic)
    - Head-up tilt (60°); standing; Valsalva maneuver
    - *Heart rate responses*: Deep breathing, hyperventilation, and standing
    - Liquid meal challenge
    - Exercise testing
    - Carotid sinus massage
    - *Plasma noradrenaline*: Supine and head-up tilt or standing
    - *Noradrenaline*: Alpha-adrenoceptors
    - Cardiac sympathetic innervations
- *Sudomotor*:
    - Central regulation thermoregulatory sweat test
    - Sweat gland response to intradermal ACh, quantitative sudomotor reflex test, and localized sweat test
    - Sympathetic skin response
- *Endocrine*:
    - *Clonidine α-2 adrenoceptor agonist*: Noradrenaline suppression; growth hormone stimulation
    - *Gastrointestinal*:
        - Video-cine-fluoroscopy, barium studies, endoscopy, gastric emptying studies, and lower gut studies
- *Renal function and urinary tract*:
    - Day and night urine volumes and sodium/potassium excretion
    - Urodynamic studies
    - Intravenous urography
    - Ultrasound examination
    - Sphincter electromyograph
- *Sexual function*:
    - Penile plethysmography
    - Intracavernosal papaverine
- *Respiratory*:
    - Laryngoscopy
    - Sleep studies to assess apnea and oxygen desaturation
- *Eye and lacrimal function*:
    - Pupil function, pharmacological and physiological
    - Schirmer's test

MANAGEMENT

Aims:

- Aimed at specific treatment of the cause and alleviation of symptoms.
- To remove the drugs or amelioration of underlying conditions that cause or aggravate the autonomic symptoms, especially in the elderly.

Treatment of ANS disorders includes:

- *Symptomatic treatment (nonpharmacological)*:
    - Only a minority require drug treatment.
    - The patient's educations are important for the management of ANS disorders.
        - Adequate intake of salt and fluids to produce a voiding volume between 1.5 and 2.5 L of urine each 24 hours is essential.
        - *Posture changes*: Stand up slowly, in stages, to decrease dizziness. Sit with legs dangling over the side of the bed for a few minutes before getting up. Flex the patient's feet and make fists with hands for a few seconds before standing up, to increase blood flow. Once standing, try tensing the leg muscles while crossing one leg over the other a few times to increase blood pressure.
        - *Elevate the bed*: Elevations of head end while sleeping and prolonged recumbency should be avoided when possible. If the patients have low blood pressure, it might help to raise the head of their bed by about 4 inches by placing blocks or risers under the legs at the head of the bed.
        - *Digestion*: Eat small, frequent meals to combat digestive problems. Increase fluids, and opt for low-fat, high-fiber foods, which can improve digestion. Restrict the foods that contain lactose and gluten.
        - *Diabetes management*: Tight blood sugar control can help lessen symptoms and help to prevent or delay the onset of new problems.
        - *Leg crossing* with maintained contraction of leg muscles for 30 seconds compresses leg veins and increases systemic resistance. Compressive garments, such as compression stockings and abdominal binders, are helpful occasionally but are uncomfortable.

- *Specific treatments*:
  - *Cardiovascular symptoms*:
    - ANS disorders can cause a number of heart rate and blood pressure problems:
      - *Medications to raise blood pressure*: If the patients feel faint or dizzy when they stand up, suggest fludrocortisone. This medication helps your body to retain salt, which helps regulate your blood pressure. Other drugs that can help to raise your blood pressure include midodrine and pyridostigmine. Droxidopa also can help to raise blood pressure. Midodrine and droxidopa can cause high blood pressure when lying down.
      - *Fludrocortisone*:
        - Enhances renal sodium conservation and increases the sensitivity of arterioles to NE
        - At doses between 0.1 mg/day and 0.3 mg BID orally, it reduces OH, but it aggravates supine hypertension.
        - Susceptible patients may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia.
      - *Midodrine*:
        - Directly acting α1-agonist, which cannot cross the blood–brain barrier
        - Duration of action: 2–4 hour. The usual dose is 5–10 mg orally TID.
        - Side effects include pruritus, uncomfortable piloerection, and supine hypertension especially at higher doses.
      - *Pyridostigmine*:
        - Parasympathomimetic and a reversible cholinesterase inhibitor which enhances ganglionic transmission and improves OH without aggravating supine hypertension. The drug is started at 30 mg BID or TID and the dose is gradually increased up to 60 mg TID
        - Its effectiveness can be enhanced, without causing supine hypertension, by combining each TID dose of pyridostigmine with midodrine 5 mg.
      - *Droxidopa*:
        - It is used to treat symptoms of low blood pressure when standing, caused by a certain medical condition (NOH).
        - *Dose*: 100 mg PO TID initially. Titrate to symptomatic response, in increments of 100 mg TID every 24–48 hour; not to exceed 600 mg TID (i.e., 1,800 mg/day).
      - *Medication to regulate heart rate*: A class of medications called beta-blockers helps to regulate your heart rate if it goes too high with an activity level.
- *A high-salt, high-fluid diet*: If your blood pressure drops when you stand up, a high-salt, high-fluid diet can help maintain your blood pressure. This is generally only recommended for severe cases of blood pressure problems, as this treatment may cause blood pressure that is too high or swelling of the feet, ankles, or legs and should not be used in patients with heart failure.
  - *Sweating*:
    - *A medication that decreases perspiration*: Glycopyrrolate (Cuvposa, Robinul, Robinul Forte, and others) can decrease sweating. Side effects can include diarrhea, dry mouth, urinary retention, blurred vision, changes in heart rate, headache, loss of taste, and drowsiness. Glycopyrrolate can also increase the risk of heat-related illness, such as heatstroke, from a reduced ability to sweat.
    - *Surgery to cut the nerves in the sweat glands*: It is also possible to remove the sweat glands but only in small areas of increased sweating, such as the palms.
  - *Gastrointestinal symptoms*:
    - *Diet changes*: The patient might need to increase dietary fiber and fluids. Fiber supplements, such as Metamucil or Citrucel, also might help. Slowly increase fiber to avoid gas and bloating.
    - *Medication to help your stomach empty*: A prescription drug called metoclopramide helps the stomach empty faster by increasing the contractions of the digestive tract.
    - *Medications to ease constipation*: Over-the-counter laxatives can help ease constipation.
    - *Medications to ease diarrhea*: Antibiotics can help treat diarrhea by preventing excess bacterial growth in the intestines, and over-the-counter antidiarrheal medication might be helpful.
  - *Urinary symptoms*:
    - *Retraining your bladder*: Following a schedule of when to drink fluids and when to urinate can help increase the patients' bladder's capacity and retrain their bladder to empty completely at the appropriate times.
    - *Medication to help empty the bladder*: Bethanechol is a medication that helps ensure complete bladder emptying. Possible side effects include headache, abdominal cramping, bloating, nausea, and flushing.

  - *Urinary assistance (catheterization)*: A tube is guided through your urethra to empty your bladder.
  - *Medications that decrease an overactive bladder*: These include tolterodine, oxybutynin, or similar medications. Possible side effects include dry mouth, headache, fatigue, constipation, and abdominal pain.
- *Sexual dysfunction*:
  - *For men with erectile dysfunction*:
    - *Medications that enable erections*: Drugs such as sildenafil, vardenafil, or tadalafil can help the patient to achieve and maintain an erection. Possible side effects include mild headache, flushing, upset stomach, and changes in color vision. If the patients have a history of heart disease, arrhythmia, stroke or high blood pressure, or any type of organic nitrates use, these medications are used with caution.
    - *External vacuum pump*: This device helps pull blood into the penis using a hand pump. A tension ring helps keep the blood in place, maintaining the erection for up to 30 minutes.
  - *For women with sexual symptoms*:
    - Vaginal lubricants to decrease dryness and make sexual intercourse more comfortable and enjoyable
    - Flibanserin for premenopausal women with low sexual desire

PROGNOSIS

- The prognosis of dysautonomia depends on several factors; individuals with chronic, progressive, generalized dysautonomia in the setting of CNS degeneration such as Parkinson's disease or MSA have a generally poorer long-term prognosis.
- Consequently, dysautonomia could be fatal due to pneumonia, acute respiratory failure, or sudden cardiopulmonary arrest.
- Autonomic dysfunction symptoms such as OH, gastroparesis, and gustatory sweating are more frequently identified in mortalities.

SPECIFIC SYNDROMES

Progressive Autonomic Failure

Introduction

- Progressive autonomic failure or IOH is a primary degenerative disorder of the central and peripheral ANSs.
- This sporadic syndrome consists of postural hypotension, impotence, bladder dysfunction, and defective sweating.
- The disorder begins in the middle decades and occurs in women more often than men.
- The symptoms can be disabling, but the disease does not shorten lifespan.
- There is a severe reduction in the density of neurons within sympathetic ganglia that results in low supine plasma NE levels and noradrenergic supersensitivity.
- Some studies have questioned the specificity of PAF as a distinct clinical entity.
- Some cases are ganglionic antibody-positive and thus represent a type of autoimmune autonomic neuropathy (AAN).
- Between 10 and 15% of cases evolve into MSA.

Pathophysiology

- The condition may be uncomplicated by other neurological manifestations (PAF), or may be associated with:
  - Parkinsonian features (PAF-P)
  - Multiple system atrophy (PAF-MSA)
- In PAF, there is a loss of cells in the ILC, loss of small myelinated fibers in the ventral roots, and loss of neurons in the dorsal vagal nuclei.
- Degeneration of sympathetic ganglia and the appearance of Lewy bodies with hyaline structures in the sympathetic ganglion cells.

Clinical Features

- Clinical features include:
  - Postural hypotension (most important)
  - Impairment of the sweating mechanism
  - Disturbances of heart rate and blood pressure control

Treatment

- Management is mostly nonpharmacological. Drugs are used for severe symptoms.
- Pharmacological treatment include fludrocortisone, midodrine, somatostatin, erythropoietin, and other vasopressor agents. However, often a patient with PAF can mitigate his or her symptoms with far less costly means.
- Compressing the legs and lower body, through crossing the legs, squatting, or the use of compression stockings, can help.
- Use of an abdominal binder is even more effective. Also, ingesting more water than usual can increase blood pressure and relieve some symptoms.

Parkinson's Disease (Details in Chapter 5)

- Autonomic disturbances are common in advanced disease.
- Difficult to distinguish from PAF-P.
- Management is symptomatic and that of underlying disease of blood pressure during procedures in patients with acute or chronic spinal cord injury is essential.

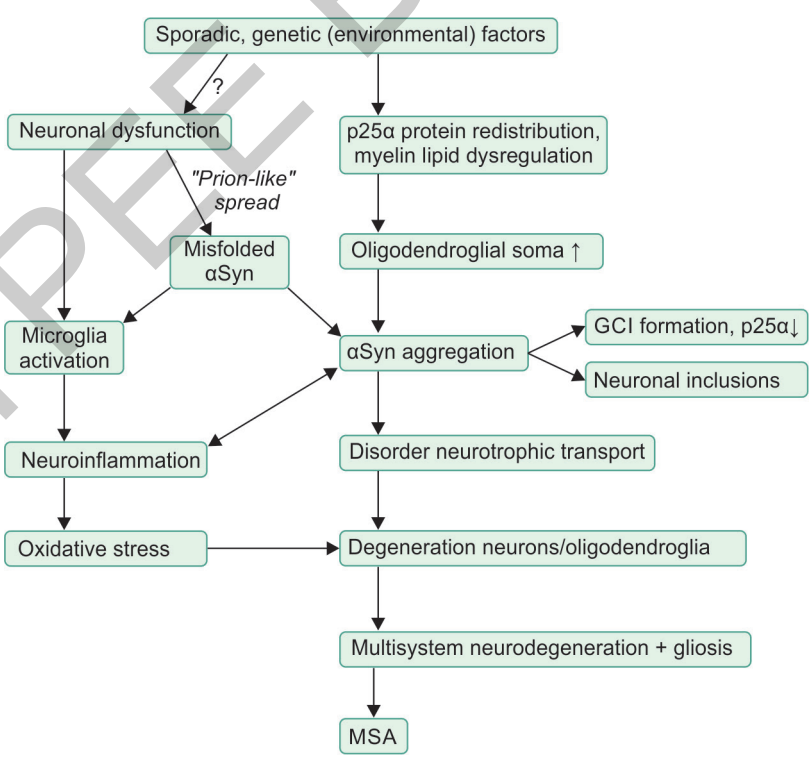
Multiple System Atrophy

Introduction

- Multiple system atrophy is a rare, adult-onset, progressive, fatal neurodegenerative disorder of uncertain etiology that presents clinically with a variable combination of autonomic, parkinsonian, cerebellar, and pyramidal features.
- It is an entity that comprises autonomic failure (OH or a neurogenic bladder) and either parkinsonism (MSA-P) or a cerebellar syndrome (MSA-C).
- The clinical diagnosis of MSA is fraught with difficulty and there are no pathognomonic features to discriminate the common parkinsonian variant (MSA-P) from PD.
- MSA-P is the more common form; the parkinsonism is atypical, in that it is usually unassociated with significant tremor or response to levodopa.
- MSA usually manifests in middle age (the median age of onset is 53), affects both sexes equally, and progresses relentlessly with a mean survival of 6–9 years.

Pathogenesis of Multiple System Atrophy (Flowchart 19.1)

- Progressive loss of neuronal and oligodendroglial cells in numerous sites in the CNS
- The etiology of the cell loss is still unknown.
- Autoimmune mechanisms and toxic agents have been suggested, but evidence for these etiologies is weak.
- No evidence of a genetic etiology
- The discovery of oligodendroglial cytoplasmic inclusions indicated that damage primarily affects the white matter.
- The chronic alterations in glial cells may impair trophic function between oligodendrocytes and axons and cause secondary neuronal damage.
- Whether the inclusions represent primary lesions or nonspecific secondary markers of cellular injury remain unknown.
- In addition to the glial cytoplasmic inclusions (GCIs), extensive myelin degeneration
- Changes in myelin may play an important role in the pathogenesis of MSA



FLOWCHART 19.1: Pathogenesis of MSA.
(GCI: glial cytoplasmic inclusion; MSA: multiple system atrophy)

Clinical Presentations

- MSA is a progressive disease characterized by the gradual accumulation of disability reflecting involvement of the systems initially unaffected.
- So, patients who present initially with extrapyramidal features commonly progress to develop autonomic disturbances, cerebellar disorders, or both **(Table 19.4)**.
- Symptomatic OH within 1 year of onset of parkinsonism predicts eventual development of MSA-P in 75% of patients.
- Characteristics that do not support the diagnosis of MSA in **Table 19.5**.

Diagnostic Criteria

- Guidelines established by the American Autonomic Society and the American Academy of Neurology for the clinical diagnosis of MSA in 1996 and 1998.
- Criteria are offered for definite, probable, and possible MSA, and for distinguishing MSA with predominant parkinsonism (MSA-P) from MSA with predominant cerebellar ataxia (MSA-C) **(Table 19.6)**.

Investigations

- The diagnosis of MSA still rests on the clinical history and neurological examination.
- Attempts have been made, however, to improve diagnostic accuracy through analysis of cerebrospinal fluid (CSF) and serum biomarkers, autonomic function tests, structural and functional neuroimaging, and neurophysiological techniques in **Table 19.7**.
- Sagittal T1 and axial FLAIR weighted brain MRI showed cerebellar and pons atrophy and the "hot cross bun" sign (white arrows) in **Figures 19.3A to C**.

TABLE 19.5: Characteristics that do not support the diagnosis of MSA.

Procedure	Nonsupporting features
History taking	• Symptomatic onset at <30 years • Onset after age 75 years • Family history of ataxia or parkinsonism • Systemic diseases or other identifiable causes for features listed in **Table 19.4** • Hallucinations unrelated to medication • Dementia
Physical examination	• Classic parkinsonian pill-rolling rest tremor • Clinically significant neuropathy • Prominent slowing of vertical saccades or vertical supranuclear gaze palsy • Evidence of focal cortical dysfunction, such as aphasia, alien limb syndrome, and parietal dysfunction
Laboratory study	• Metabolic, molecular genetic, and imaging evidence of alternative cause of features listed in **Table 19.7** • White matter lesions suggesting multiple sclerosis

(MSA: multiple system atrophy)

TABLE 19.4: Clinical domains and features in the diagnosis of MSA.

Domain	Criterion	Feature
Autonomic and urinary dysfunction	• Orthostatic fall in blood pressure (by 30 mm Hg systolic or systolic or 10 mm Hg diastolic) Or • Persistent urinary incontinence with erectile dysfunction in men or both	• Orthostatic hypotension 15 mm Hg diastolic (by 20 mm Hg systolic or 10 mm Hg diastolic) • Urinary incontinence or incomplete bladder emptying
Parkinsonism	• Bradykinesia plus • Rigidity Or • Postural instability Or • Tremor	• Bradykinesia (progressive reduction in speed and amplitude of voluntary movements during repetitive actions) • Rigidity • Postural instability (loss of primary postural reflexes) • Tremor (postural, resting, or both)
Cerebellar dysfunction	• Gait ataxia plus • Ataxic dysarthria Or • Limb ataxia Or • Sustained gaze-evoked nystagmus	• Gait ataxia (wide based stance with irregular steps) • Ataxic dysarthria • Limb ataxia • Sustained gaze-evoked nystagmus
Corticospinal tract dysfunction	No defining features	Extensor plantar responses with hyperreflexia

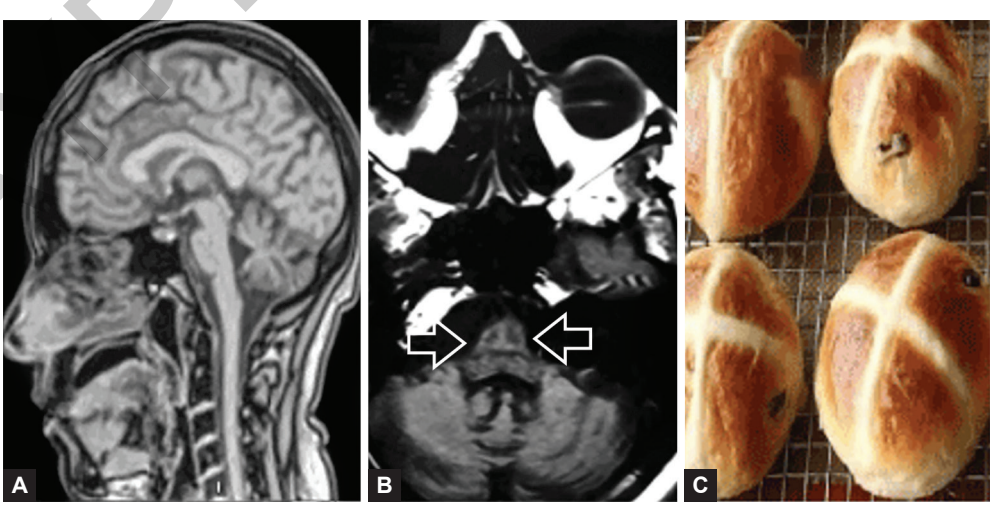
(MSA: multiple system atrophy)

TABLE 19.6: Diagnostic criteria of MSA.	
Types	**Criterion**
Possible MSA-P	Criterion for parkinsonism plus two features from separate other domains. A poor levodopa response qualifies already as one feature; hence only one additional feature is required
Possible MSA-C	Criterion for cerebellar dysfunction plus two features from separate other domains
Probable MSA-P	Criterion for autonomic failure/urinary dysfunction plus poorly levodopa responsive parkinsonism
Probable MSA-C	Criterion for autonomic failure/urinary dysfunction plus cerebellar dysfunction
Definite MSA	Pathological confirmation: High density of α-synuclein-positive GCIs associated with degenerative changes in the nigrostriatal (SND) and olivopontocerebellar pathways (OPCA)

(GCI: glial cytoplasmic inclusion; MSA: multiple system atrophy)

TABLE 19.7: Investigations of MSA.	
Cardiovascular autonomic function tests	• Orthostatic hypotension (20/10 mm Hg systolic/diastolic blood pressure drop) • Impaired reflex tachycardia • Impaired heart rate variability impaired • Valsalva maneuver
Clonidine challenge test	Impaired rise of plasma noradrenaline upon standing impaired release of growth hormone (controversial)
Thermoregulatory sweat test (TST), quantitative sudomotor axon reflex test (QSART)	Sudomotor dysfunction (an-/hypohidrosis) due to pre- and postganglionic sympathetic failure
Sympathetic skin response	Abnormal or absent
CSF external anal sphincter	Increased neurofilament protein level
EMG	Denervation (nonspecific)
CCT	Unhelpful
MRI (1.5 Tesla)	Basal ganglia abnormalities (putaminal atrophy/hyperintense putaminal rim/putaminal hypointensity, infratentorial signal change—hot cross bun sign), cerebellar and/or brain stem atrophy
IBZM-SPECT	Reduced striatal dopamine D2 receptor binding
FDG-PET	Reduced striatal, frontal, and infratentorial metabolism

[CCT: creatinine clearance test; CSF: cerebrospinal fluid; EMG: electromyography; FDG-PET: fludeoxyglucose-18 positron emission tomography; IBZM-SPECT: (^{123}I)iodobenzamide single-photon emission computed tomography; MSA: multiple system atrophy]



FIGS. 19.3A TO C: (A) Sagittal T1*-weighted brain MRI showing cerebellar and pontine atrophy. (B) Axial FLAIR* exhibit the "hot cross bun" sign in the pons and cerebellar atrophy (arrows). (C) Hot cross bun served during Holy Week.

(FLAIR: fluid-attenuated inversion recovery)

Management of Multiple System Atrophy

(Above → More details in treatment of ANS disorders)

- Because of the small number of randomized controlled trials, the practical management of MSA is largely based on empirical evidence (↔) or single randomized studies ( ), except for a few randomized controlled studies of midodrine ( ).
- The present recommendations are summarized in **Box 19.1**.

BOX 19.1 Management of MSA.

- *Pharmacotherapy*:
  - *For akinesia rigidity*:
    - Levodopa up to 800–1,000 mg/day, if tolerated (↔)
    - Dopamine agonists as second-line antiparkinsonian drugs (dosing as for PD patients) (↔)
    - Amantadine as third-line drug, 100 mg up to three times daily (↔)
  - *For focal dystonia*:
    - Botulinum toxin A (↔)
  - *For orthostatic hypotension*:
    - Head-up tilt of bed at night (↔)
    - Elastic stockings or tights (↔)
    - Increased salt intake (↔)
    - Fludrocortisone 0.1–0.3 mg/day (↔)
    - Ephedrine 15–45 mg TID (↔)
    - L-threo-DOPS (300 mg BID) (↔)
    - Midodrine 2.5–10 mg TID ( )
  - *For postprandial hypotension*:
    - Octreotide 25–50 mg SC 30 minutes before a meal (↔)
  - *For nocturnal polyuria*:
    - Desmopressin (spray: 10–40 µg/night or tablet: 100–400 µg/night) (↔)
  - *For bladder symptoms*:
    - Oxybutynin for detrusor hyperreflexia (2.5–5 mg BID–TID) (↔)
    - Intermittent self-catheterization for retention or residual volume >100 mL (↔)
- *Other therapies*:
  - Physiotherapy (↔)
  - Speech therapy (↔)
  - Occupational therapy (↔)
  - PEG (rarely needed in late stage) (↔)
  - Provision of wheelchair (↔)
  - CPAP ( ) [rarely tracheostomy (↔)] for inspiratory stridor

(CPAP: continuous positive airway pressure; L-threo-DOPS: L-threo-dihydroxyphenylserine; PEG: percutaneous endoscopic gastrostomy)

Spinal Cord Lesions (Details in Chapter 33)

Spinal cord lesions from any cause may result in focal autonomic deficits or autonomic hyperreflexia:

- *Autonomic dysreflexia* describes a dramatic increase in blood pressure in patients with traumatic spinal cord lesions above the C6 level, often in response to stimulation of the bladder, skin, or muscles.
- Spinal cord lesions from any cause may result in focal autonomic deficits or autonomic hyperreflexia (e.g., spinal cord transection or hemisection) affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions.
- Quadriparetic patients exhibit both supine hypertension and OH after upward tilting.
- Autonomic dysreflexia describes a dramatic increase in blood pressure in patients with traumatic spinal cord lesions above the C6 level, often in response to stimulation of the bladder, skin, or muscles.
- Suprapubic palpation of the bladder, a distended bladder, catheter insertion, catheter obstruction, or urinary infection are common triggers.
- Associated symptoms can include flushing, headache, or piloerection.
- Potential complications include intracranial vasospasm or hemorrhage, cardiac arrhythmia, and death.
- In patients with supine hypertension, BP can be lowered by tilting the head upward. Vasodilator drugs may be used to treat acute elevations in BP. Clonidine can be used prophylactically to reduce the hypertension resulting from bladder stimulation.

Autoimmune Autonomic Neuropathy

- Presents with the subacute development of autonomic disturbances with:
  - OH
  - Enteric neuropathy (gastroparesis, ileus, constipation/diarrhea)
  - Cholinergic failure (loss of sweating, sicca complex, and a tonic pupil)
- Autoantibodies against the ganglionic ACh receptor (A3 AChR) are present and are now considered to be diagnostic.
- Beneficial response to plasmapheresis or intravenous immune globulin has been documented.
- Treatment is symptomatic based on the involved systems.
  - Control of OH is typically most important.

- Symptomatic management of OH, gastroparesis, and sicca symptoms is essential.
- A dramatic clinical response to repeated plasma exchange combined with immunosuppression was described in one patient with longstanding AAN.
- Recovery is slow and often incomplete.

Postural Orthostatic Tachycardia Syndrome

- Characterized by symptomatic orthostatic intolerance (not OH) and by either an increase in heart rate to >120 beats/min or an increase of 30 beats/min withstanding that subsides on sitting or lying down.
- Women are affected approximately five times more often than men, and most develop the syndrome between the ages of 15 and 50.
- Approximately half of affected patients report an antecedent viral infection.
- Syncopal symptoms (lightheadedness, weakness, and blurred vision) combined with symptoms of autonomic overactivity (palpitations, tremulousness, and nausea) are common. Recurrent unexplained episodes of dysautonomia and fatigue also occur.
- The pathogenesis is unclear in most cases; hypovolemia, deconditioning, venous pooling, impaired brainstem regulation, or β-receptor supersensitivity may play a role.
- Expansion of fluid volume and postural training are initial approaches to treatment.
- If these approaches are inadequate, then midodrine, fludrocortisone, phenobarbital, beta-blockers, or clonidine may be used.

Hereditary Sensory and Autonomic Neuropathies

- There are five known hereditary sensory and autonomic neuropathies (HSAN I–V) which are inherited disorders.
- The most important ones are HSAN I and HSAN III (Riley–Day syndrome; familial dysautonomia).
- HSAN I is dominantly inherited and often presents as a distal small-fiber neuropathy (burning feet syndrome).
- The responsible gene, on chromosome 9q, is designated *SPTLC1*. SPTLC is an important enzyme in the regulation of ceramide.
- HSAN III, an autosomal recessive disorder of infants and children that occurs among Ashkenazi Jews, is much less prevalent than HSAN I.
- Decreased tearing, hyperhidrosis, reduced sensitivity to pain, areflexia, absent fungiform papillae on the tongue, and labile BP may be present. Episodic abdominal crises and fever are common.
- The defective gene, named *IKBKAP*, is also located on the long arm of chromosome 9.

Acute Autonomic Syndromes

- An autonomic storm is an acute state of sustained sympathetic surge that results in variable combinations of alterations in blood pressure and heart rate, body temperature, respiration, and sweating.
- Causes of autonomic storm are brain and spinal cord injury, toxins and drugs, autonomic neuropathy, and chemodectomas (e.g., pheochromocytoma).
- Management of autonomic storm includes ruling out other causes of autonomic instability, including malignant hyperthermia, porphyria, and epilepsy.
  - Sepsis and encephalitis need to be excluded with appropriate studies. An electroencephalogram (EEG) should be done to detect epileptiform activity; MRI of the brain and spine is often necessary.
  - The patient should be managed in an intensive care unit.
  - Management with morphine sulfate (10 mg every 4 hour) and labetalol (100–200 mg twice daily) has worked relatively well.
  - Treatment may need to be maintained for several weeks.
  - For chronic and milder autonomic storm, propranolol and/or clonidine can be effective.

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Fundamentals in CLINICAL NEUROLOGY

This book is ideally designed for the needs of the student who is just beginning his study of clinical neurology. This book reviewed the fundamentals of clinical neurology as they apply to everyday clinical practice. The clinical characteristics of the disease are clearly linked to anatomy and physiology. Nevertheless, they are discussed in far more depth than the clinical aspects of neurology, these fundamental issues belong in a book of this competence. This presentation provides a medical student at the end of his sophomore year or just starting his junior year with a difficult review of his previous work and just enough clinical information to whet his appetite without overwhelming him. The method of assessing a patient to detect signs and symptoms of neurological disease is addressed as well.

Key Features

- This textbook emphasizes high-yield knowledge in clinical neurology for easy memory retention
- Emphasizes high-yield knowledge in clinical neurology for easy memory retention
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