Autonomic NS Disorders (GENERAL)

ETIOLOGICAL CLASSIFICATION

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N.B. most frequent autonomic dysfunction encountered in medical practice is pharmacological (esp. antihypertensives and psychotropic drugs).

DIFFUSE AUTONOMIC FAILURE (PANSAUTONOMIA)

I. Preganglionic autonomic failure (CENTRAL neurodegenerative diseases)
   1. Multiple system atrophy (Shy-Drager syndrome) – degeneration of central autonomic control nuclei – autonomic failure is severe!
   2. Parkinson’s disease

II. Ganglionic and postganglionic disorders (PERIPHERAL neurodegenerative disorders)
   Post autonomic failure (e.g. chronic preganglionic autonomic insufficiency) see p. Veg3
   Acute panautoniasia
   1) Guillain-Barré syndrome
   2) acute paroxysmal neuropathies
   3) acute intermittent porphyria
   4) drugs (vincristine, Taxol, cisplatinum)
   5) toxins (thallium, acrylamide, Vacor (rat poison))
   6) tetanus – up to 40% patients in ICU may suffer arrhythmias → cardiac arrest.

Chronic small-fiber (postganglionic) neuropathies:
   1) diabetics - most common cause of autonomic neuropathy in developed world!
   2) amyloidosis
   3) alcoholic neuropathy

Hereditary:
   HSAN, esp. familial autoniasia (Riley-Day syndrome) see p. PN3
   Fabry disease
   Subacute or chronic sensory and autonomic ganglionopathies:
   Paraneoplastic
   Sygmon syndrome
   Other peripheral neuropathies:
   Infections (HIV)
   Connective tissue disease (SLE)
   Metabolic-nutritional (alcohol, uremia, vitamin B1 deficiency)

CHOLINERGIC DISYNAPTOMAS

I. Neuromuscular transmission defect
   1. Botulism (acute)
   2. Lambert-Eaton myasthenic syndrome (chronic)

II. No neuromuscular transmission defect
   1. Acute cholinergic neuropathy
   2. Dopa/min-hydroxylase deficiency see p. Veg3
   3. Idiopathic orthostatic hypotension see p. Veg3

Autonomic Dysfunction SECONDARY TO FOCAL CNS DISEASE

Telencephalon
   1. Stroke (e.g. ischemic damage to insula, cingulate and paracentral cortices)
   2. Temporal seizures

Diencephalon (esp. hypothalamus):
   1. Wernicke encephalopathy
   2. Episodic hyperhidrosis with hypothermia – idopathic or as manifestation of corpus callosum agenesis
   3. Paroxysmal autonomic hyperreactivity (s. diencephalic seizures – misnomer! – EEG shows no ictal activity) - majority of cases due to severe closed head injuries marked by episodic increases in ICP and acute hydrocephalus following SAH.
   4. Fatal familial insomnia
   5. Iatrogenic
   6. Neuropathic malignant syndrome
   7. Serotonin syndrome

Brain stem:
   1. Vertebrobasilar disease (e.g. TIA in basilar artery territory, lateral medullary infarction s. Wallenberg syndrome)
   2. Tumors
   3. Syringobulbia
   4. Arnold-Chiari (type I malformation)
   5. Inflammation (multiple sclerosis, polyomyelitis)

Spinal cord
   1. Trauma (spinal cord transaction above T6, i.e. above major splanchnic sympathetic outflow) - autonomic dysreflexia (s. paroxysmal autonomic hyperreflexia) – massive reflex activation of sympathetic outflow below lesion level. see p. Spinal
   2. Syringomyelia
   3. Tetanus
   4. Stuff-person syndrome

N.B. multiple sclerosis may affect autonomic pathways at spinal cord, brain stem, or diencephalon!

TOPGRAPHIC / ORGAN-SPECIFIC DISORDERS

1. Pupils
   see p. Eyed >>

2. Vasomotor and sudomotor disorders of face
   1) generalized sweating and flushing – in
   – idiopathic hemifacial hyperhidrosis (associated with hypertrphy of sweat glands)
   – bilateral cervicothoracic sympathectomy (reinnervation of superior sympathetic ganglion by preganglionic sympathetic fibers destined for sweat glands);

Other peripheral neuropathies:
   In: Hereditary:
   - HSAN, esp. familial autoniasia
   - Paraneoplastic
   - Sygmon syndrome
   Other peripheral neuropathies:
   - Infections (HIV)
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Major NS Disorders (General)

- local damage to autonomic fibers traveling with CN5 (e.g. parotid or submaxillary gland surgery, V3 censure) – reinervation of sweat glands and blood vessels by parasympathetic vasodilator fibers destined for salivary glands;
- peripheral neuropathies (most frequently diabetes mellitus)

2) Pourfour du Petit syndrome (reverse of Horner’s syndrome) – dilated pupil + flushing + hyperhidrosis – due to sympathetic hyperactivity (frequently following injuries); check that damage sympathetic plexus around carotid artery).
3) harlequin syndrome – sudden flushing and sweating on one side of face (due to lesions in contralateral central or peripheral sympathetic nervous system pathways).
4) cluster headache – accompanied by ipsilateral parasympathetic hyperactivity (lacrimation and nasal discharge), sympathetic overactivity (forehead sweating), and ocular sympathetic paralysis (miosis and ptosis).

3. Vasomotor disorders of limbs

1) Raynaud’s phenomenon
2) acrocyanosis
3) livedo reticulata
4) erythromelalgia
5) vasomotor paralysis – in lesions of sympathetic pathways

4. Subautonomic disorders of limbs

N.B. sweat glands are innervated by noradrenergic sympathetic fibers (mediating emotional responses) and cholinergic sympathetic fibers (thermal sweating).

AXILLARY eccrine sweat glands are activated by thermal stimuli, whereas PALMAR & PLANTAR glands by emotional stimuli

Localised hyperhidrosis – due to injury to:
- spinal cord (e.g. syringomyelia)
- peripheral nerves (e.g. partial median or sciatic nerve injury)
- eccrine sweat glands.

Essential hyperhidrosis (may be familial) affects axillary, palmar, and plantar regions.

Generalised hyperhidrosis – secondary to infections, malignancies, neuroendocrine disorders (pheochromocytoma, thyrotoxicosis, acromegaly, cancer, anxiety, hypopituitarism, hypothyroidism, cholinergic agents).

Congenital insensitivity to pain and analgesia – presents in early infancy (affects boys much more frequently than girls) – do not perspire – episodes of high fever related to warm environmental temperatures; lack of pain perception – frequent burns and traumatic injuries; normal intelligence; nerve biopsy - almost total absence of unmyelinated nerve fibers (for pain, temperature, and autonomic functions).

Regional pain syndromes (causalgia, reflex sympathetic dystrophy, etc). see p. 520


7. Sexual dysfunction
- erectile dysfunction, ejaculation dysfunction.

CLINICAL FEATURES

- symptoms are extremely varied!
- Pure autonomic failure with no other neurological deficits is rare!

I. Eyes – decreased lacrimation.

II. Cardiovascular system – baroreflex dysfunction: 1) orthostatic hypotension + syncope – most severely disabling feature! N.B. no compensatory tachycardia!
2) supine hypertension
3) fixed heart rate regardless of posture
4) postprandial hypotension
5) acral vasomotor changes

Gastrointestinal dysmotility

III. Gastrointestinal system

1) abnormal motility – constipation (typical symptom!), diarrhea, nausea, postprandial vomiting, belching, appetite loss, early satiety.
2) glandular secretion↓
3) vomiting, bloating, nausea, constipation (typical symptom!)
4) decreased salivation.
5) decreased lacrimation.

IV. Urinary bladder – hesitancy, poor stream production, increased intervals between micturition, dribbling.

V. Sexual function – male impotence

VI. Thermoregulation – altered sweating: hyperhidrosis or hypohidrosis (→ heat intolerance, flushing, heat-stroke symptoms).

MAJOR CLINICAL MANIFESTATIONS in generalized autonomic failure syndromes:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Postural Hypotension</th>
<th>GU Dysfunction</th>
<th>GI Dysfunction</th>
<th>Sweating Deficit</th>
<th>Other Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>++</td>
<td>+</td>
<td>±</td>
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<td>Postprandial hypotension</td>
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<tr>
<td>Alcoholism</td>
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<td>Tachycardia</td>
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<tr>
<td>Anyhidrosis</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
<td>Desequibrated sensory loss</td>
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<tr>
<td>Diabetes mellitus</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>Distal neuropathy</td>
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<tr>
<td>Familial dysautonomia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td></td>
<td>Abdominal crises, fevers, sensitivity to pain</td>
</tr>
<tr>
<td>Holmes–Adie syndrome</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
<td>Toxic pupils, areflexia, suprahyoid hypotension</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td>Parkinsonism and/or cerebellar dysfunction</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
<td>Treming may be increased</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td>Rigidity, gaze pareses</td>
</tr>
<tr>
<td>Pure autonomic failure</td>
<td>+++</td>
<td>+++</td>
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</tbody>
</table>

DIAGNOSIS
MRI – for focal or organ-specific autonomic syndromes.

EMG – denervation in lesions of conus/cauda equina and in multiple system atrophy.

Nerve conduction velocities (NCVs) – useful in peripheral neuropathy.

Pharmacological tests evaluate response of effector organs:

- **DECREASED** – due to denervation supersensitivity (manifestation of postganglionic failure, vs. preganglionic).
- **INCREASED** – due to denervation supersensitivity (manifestation of postganglionic failure, vs. preganglionic).

**Pupil**

4% COCAINE, 1% HYDROXYAMPHETAMINE tests. see p. Eyelids

**Cardiovascular system**

Evaluation of cardiac VAGAL innervation:

1. **Heart rate response to deep breathing** (best noninvasive test for assessment of cardiac vagal innervation) – heart rate increases during inspiration and decreases during expiration;
   - laboratory measures of heart rate variability include peak-to-trough amplitude during single breath, standard deviation of ECG RR intervals during 1 minute, statistical measures such as mean square successive difference, expiratory-inspiratory ratio (E/I ratio), mean circular resultant.
   - respiratory sinus arrhythmia is abolished by atropine.

2. **Heart rate response to Valsalva maneuver** – assesses baroreceptor reflex – performed by blowing through mouthpiece connected to mercury manometer (column of manometer maintained at 40 mmHg) for 15-20 seconds with subject sitting or supine; normal response has four phases:
   - **Phase 1 (onset of straining)** – transient rise in arterial pressure (due to aortic compression) + decrease in heart rate.
   - **Phase 2** – gradual fall in blood pressure (due to increased sympathetic discharge) + increase in heart rate.
   - **Phase 3 (cessation of straining)** – sudden brief fall in blood pressure (due to increased capacitance of pulmonary bed) + heart rate increases further.
   - **Phase 4 (recovery)** – increase in blood pressure above resting value ("overshoot" – due to persistent vasoconstriction and increased cardiac output) + compensatory bradycardia.
   - phases 1 & 3 reflect mechanical factors (changes in intrathoracic and intraabdominal pressure).
   - phases 2 & 4 are consequence of sympathetic, vagal, baroreflex interactions.
   - Valsalva ratio (maximum phase II tachycardia/minimum phase IV bradycardia) – reflects integrity of entire baroreceptor reflex arc.

3. **Heart rate response to postural change** (“30:15 ratio”) – heart rate changes that occur during first 30 seconds of standing result mostly from modification of cardiovagal activity and are blocked by atropine:
   - **Heart rate increases** sharply on standing, peaking at ≈ 12 seconds (≈ 15th beat) → progressively slows* until ≈ 20 seconds after standing (30th RR interval is longest) → gradually returns again.
   - *due to reflex activation of efferent cardiac vagal fibers; bradycardia is reduced in abnormal cardiovagal function.
   - 30:15 ratio = longest RR interval around 30th beat / shortest RR interval around 15th beat (RRmax 30 /RRmin 15 ratio)
A) 34 y.o. male with autonomic failure.

B) 25 y.o. male with neurally mediated syncope.

Evaluation of cardiovascular sympathetic innervation

1. Cardiovascular response to postural change – changes in blood pressure and heart rate induced by passive tilt or active standing – most useful test of sympathetic function!
   - upright tilt ≥ 60° → transient reduction in systolic, diastolic, mean blood pressures, heart rate increases by 10-20 beats per minute → recovery within 1 minute.
   - adrenergic failure → marked reduction in systolic, diastolic, and pulse pressure with no recovery + inadequate compensatory tachycardia.

   - adrenergic failure → profound decrease of blood pressure in phase 2, absence of blood pressure “overshoot” in phase 4.

3. Hemodynamic response to physical / emotional perturbations:
   - a) immersion of hand in cold water for 1 minute (cold pressor test) – afferent pathway is spinothalamic (distinct from afferent limb of baroreceptor reflex arc!); efferent pathway is sympathetic.
   - b) isometric exercise (e.g. sustained handgrip maneuver)
   - c) emotional stress (e.g. mental arithmetic)
   - normal subjects → increases in diastolic pressure > 15 mmHg and in heart rate > 10 beats per minute.


5. Plasma norepinephrine (NE) in supine and standing positions (for orthostatic hypotension).
   - in postganglionic failure, resting levels of NE are subnormal (vs. preganglionic failure → [NE] normal).
   - in normal subjects, plasma [NE] doubles with assumption of upright posture (vs. pre- or post-ganglionic sympathetic failure – absent response).
   - infusion of EDROPHONIUM (cholinomimetic agent) or TYRAMINE (indirect sympathomimetic agent) → release of NE stores.

6. Changes in response to pressor or depressor drugs.
   - pressor response to infusion of α-adrenergic agonists; postganglionic autonomic failure → decreased threshold for pressor effects, diastolic blood pressure increases≥ 20 mmHg (denervation supersensitivity).

Skin

1. Thermoregulatory sweat test – by raising body temperature with external heating source → change in color of indicator powder (e.g. iodine with starch, guanizarin, alizarin-red) in response to rise in core body temperature – evaluates distribution of sweating; test abnormal in both pre- and post-ganglionic failure.

2. Postganglionic sudomotor function – measuring sweat output after:
   - a) iontophoresis of cholinergic agonist – quantitative sudomotor axon reflex test (QSART).
   - b) intradermal injection of cholinergic agonists (PILOCARPINE, NICOTINE, METHACHOLINE).

3. Intradermal injection of HISTAMINE – ”TRIPLE RESPONSE” (erythema, flare, wheal) through axon reflex (via nociceptive C-fiber); loss of histamine flare = loss of nociceptive C axons:
   - familial dysautonomia
   - peripheral neuropathies affecting sympathetic nerves.

4. Sympathetic skin potential (s. peripheral autonomic surface potential) – electrodermal activity (slow change in electrical potential of skin) generated by sweat production – occurs spontaneously
and can be evoked (by unexpected noise, deep inspiration, electrical stimuli); autonomic failure → absence of sympathetic skin response (limited specificity + no localizing value).

5. Sweat imprint – formed by secretion of active sweat glands into plastic or silicone mold in response to iontophoresis of cholinergic agonist (to determine sweat gland density, sweat droplet size, sweat volume per unit of area).

**PREGANGLIONIC** cause of anhidrosis → abnormal thermoregulatory sweat test + normal postganglionic function.

**POSTGANGLIONIC** cause of anhidrosis → abnormal thermoregulatory sweat test + abnormal postganglionic function.

### Urinary bladder

**Postvoid residual volume** (measurements of bladder volume):
- **large bladder volumes** – lower motor neuron bladder or sensory denervation;
- **small bladder volumes** – upper motor neuron or spastic bladder.

#### Differentiation of **PREGANGLIONIC** versus **POSTGANGLIONIC** pandysautonomia

<table>
<thead>
<tr>
<th>Preganglionic (e.g. multiple system atrophy)</th>
<th>Postganglionic (e.g. small fiber neuropathy)</th>
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<tbody>
<tr>
<td>Plasma norepinephrine normal</td>
<td>↓ NE response to standing</td>
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<tr>
<td>NE response to KDOPHORESIS normal</td>
<td>normal</td>
</tr>
<tr>
<td>Blood pressure response to TYPRAMINE increases</td>
<td>NE response to standing</td>
</tr>
<tr>
<td>Blood pressure response to NE increases, normal threshold</td>
<td>Vasomotor responses</td>
</tr>
<tr>
<td>Thermoregulatory sweat responses impaired</td>
<td></td>
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<tr>
<td>Cholinergic sweat response normal</td>
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<td>Horner's syndrome:</td>
<td></td>
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<tr>
<td>Response to PHENYLEPHRINE diluted pupil</td>
<td>no response</td>
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<tr>
<td>Response to diluted α-agonist no response</td>
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<tr>
<td>Adie's pupil: Response to diluted muscarinic agonist</td>
<td>pupil constricts (denervation supersensitivity)</td>
</tr>
</tbody>
</table>

**BIBLIOGRAPHY** for ch. “Autonomic NS disorders” → follow this [LINK] >>