Autonomic Neuropathy

Autonomic neuropathy affects the autonomic neurons of either or both of the parasympathetic and sympathetic nervous systems. They are usually accompanied by somatic neuropathy but can be autonomic only. Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction.\[1\]

Several syndromes and diseases exhibit autonomic neuropathies and there is a wide variety of clinical features and presentations.\[2\] In some patients the features are subclinical, whereas in others the dysfunction leads to significant disability. It is important to recognise and correctly diagnose autonomic neuropathy because successful treatments and management can be offered.

Pathophysiology

As might be expected, various pathophysiological processes are involved depending on the particular cause.\[3\] Although loss of somatic C fibres is associated with autonomic deficits, there is now known to be a more selective involvement of fibres in some conditions. Somatic and autonomic C fibre involvement is found in diabetic neuropathies. The exact mechanism has not been worked out for all conditions and causes. However, the following have been identified and may be involved:

- Single gene defects.
- Accumulation of toxins.
- Autoantibodies. For example:
  - Autonomic ganglionic acetylcholine receptor antibody (pandysautonomia).
  - Ganglionic receptor antibodies (postural orthostatic tachycardia syndrome).
  - Ganglioside autoantibodies (Guillain-Barré syndrome).
  - Antibodies to presynaptic channels (Eaton-Lambert syndrome).
  - Antineuronal antibodies (coeliac disease, paraneoplastic autonomic neuropathy).
  - Prevention of presynaptic acetylcholine release (botulism).
  - Accumulation of toxic metabolites (for example, in liver disease).
  - Postganglionic abnormalities (connective tissue diseases, systemic lupus erythematosus (SLE), rheumatoid arthritis).
  - Accumulation of glycolipids (Anderson-Fabry disease).

Causes

There is a long list of causes including hereditary and acquired conditions.\[4\] The full spectrum includes:

- Ageing: postural hypotension and disordered thermoregulation are common in the elderly.
- Causes linked with systemic diseases include:
  - Diabetic autonomic neuropathies\[5\]
  - Alcoholic neuropathy
  - Subacute combined degeneration
  - Liver disease
  - Chronic kidney disease
  - Amyloidosis

- Infectious causes: eg, human immunodeficiency virus (HIV), Lyme disease, leprosy, Chagas' disease.
- Toxic causes: eg, vincristine, cisplatin, amiodarone, pyridoxine overdose, thallium poisoning, paclitaxel.
- Immune-mediated causes:
  - Rheumatoid arthritis, SLE, Sjögren's syndrome, systemic sclerosis, autoimmune thyroiditis
  - Neuropathy related to inflammatory bowel disease
  - Postural orthostatic tachycardia syndrome (POTS)\[6\]
  - Guillain Barré syndrome
  - Chronic inflammatory demyelinating neuropathy
  - Acute pandysautonomia
  - Acute cholinergic pandysautonomia
  - Eaton-Lambert syndrome
  - Holmes-Adie syndrome
  - Paraneoplastic autonomic neuropathy

- Hereditary causes: eg, Anderson-Fabry disease, Tangier disease, multiple endocrine neoplasia (type 2b).
- Idiopathic causes: chronic idiopathic anhidrosis.

Epidemiology
In general, these can occur in men and women at any age, but the epidemiology will depend on the particular cause. Some causes are very rare. However, one of the most common causes of autonomic neuropathy is likely to be diabetes mellitus. Progressive autonomic failure usually becomes apparent in the sixth decade of life. Typically it manifests with genitourinary symptoms and orthostatic hypotension but without somatic symptoms.

**Presentation**

Autonomic nervous system dysfunction may present with a variety of symptoms. Orthostatic intolerance (including orthostatic hypotension or tachycardia) and sweating abnormalities (increased or decreased sweating) are common problems. [7]

**History**

Autonomic nerve fibres are affected in most symmetrical peripheral neuropathies; however, involvement is often subclinical or mild. [4] Usually the onset of symptoms is slow and insidious. Occasionally the onset can be acute and dramatic in the acute forms. Usually there is sympathetic and parasympathetic dysfunction. Orthostatic or postural hypotension is the most commonly recognised symptom, but there is a wide variety of other possible symptoms. A family history and drug history may also be important.

### Possible symptoms of autonomic neuropathy

#### Sweating
- There may be no sweating or reduced sweating (anhidrosis and hypohidrosis), but excessive sweating (or hyperhidrosis) can occur as a compensatory mechanism.

#### Temperature regulation
- Hypothermia and hyperpyrexia can result from disruption of the various temperature regulatory mechanisms. Sweating, shivering and vasoactive reflexes can be affected.

#### Face
- Pallor.
- Reduced or absent sweating.

#### Vision
- Blurring of vision.
- Tunnel vision.
- Light sensitivity.
- Difficulty focusing.
- Reduced lacrimation.
- Gradual reduction of pupillary size.

#### Cardiovascular
- Orthostatic hypotension (often associated with or exacerbated by eating, exercise and raised temperature).
- Other orthostatic symptoms (for example, nausea, palpitations, light-headedness, tinnitus, shortness of breath).
- Syncope (may occur with micturition, defecation).
- Inability to stand without syncope (severe cases).
- Arrhythmias.
- Supine hypertension.
- Loss of diurnal variation in blood pressure (BP).

#### Respiratory
- In those with diabetes, reduced bronchoconstrictor reflexes have been detected (contributing to reduced responses to hypoxia).

#### Gastrointestinal
- Constipation.
- Diarrhoea.
- Incontinence.
- Dry mouth.
- Disturbance of taste.

#### Sexual
- Impotence.
- Ejaculatory failure.
- Female sexual dysfunction.

#### Feet
- Burning sensation.
- Hair loss.
- Pruritus.
- Dry skin.
- Pale, cold feet.
• Worsening of symptoms at night.

Examination
There may be features on general examination which point to a specific disease. The neurological examination should be detailed and thorough, incorporating motor and sensory examination. There are a few specific techniques which can be used for certain specific autonomic abnormalities.[8]

General examination

• Stigmata of liver disease.
• Skin conditions (for example, Lyme disease and leprosy).
• Signs of connective tissue diseases (for example, rheumatoid arthritis, SLE, Sjögren's syndrome).
• Features of unusual conditions (such as Anderson-Fabry disease and amyloidosis).

Neurological examination

• Motor examination (power, tone, co-ordination and reflexes).
• Sensory examination (all modalities including proprioception).
• It is important to identify stocking pattern of sensory loss (concurrent somatic neuropathy).

More specific examination
Looking for signs of autonomic dysfunction:

Testing for abnormalities of BP regulation

• Look for postural drop of systolic BP >20 mm Hg (lying and sitting) or >10 mm Hg with presyncopal symptoms.[9]
• Measure BP after isometric exercise (in the opposite arm). BP should increase by >16 mm Hg in the opposite arm.
• Measure postprandial BPs to detect >20 mm Hg 20 minutes after meal (abnormal).
• Detect >15 mm Hg diurnal variation of BP (suggests autonomic neuropathy).
• Measure BP after hand immersion in ice cold water for one minute. Contralateral arm shows >10 mm Hg diastolic drop as normal response.
• Detection of normal pulse variation with breathing (increases inspiration, decreases during expiration).
• BP recovery after Valsalva manoeuvre.[10]

Skin examination

• Palms, soles and axillae (establish whether there is sweating).
• Note whether there is skin shrivelling after prolonged immersion in water.

Eye examination

• Pupil responses (to light and accommodation).
• Look for Horner’s syndrome.
• Examine for effects of reduced eye secretions (cornea).

Mouth examination

• Look for excessive dental decay (an effect of dry month).

Abdominal examination

• Looking for an enlarged bladder.

Differential diagnosis

• Alcohol-related neuropathy
• Cauda equina syndrome
• Charcot-Marie-Tooth syndrome
• Hereditary motor and sensory neuropathies
• Conus medullaris syndrome
• Parkinson's disease
• Spinal cord trauma
• Surgical sympathectomy

Patients with Parkinson's disease can have autonomic dysfunction (constipation and urinary retention) but unlike peripheral autonomic neuropathies have extrapyramidal dysfunction (akinesia, tremor, rigidity).
Investigations
Non-invasive measures of cardiovascular parasympathetic function involve the assessment of heart rate variability. Measures of cardiovascular sympathetic function assess the blood pressure response to physiological stimuli.

Tilt-table testing, with or without pharmacological provocation, has become an important tool in the assessment of a predisposition to neurally mediated (vasovagal) syncope, postural tachycardia and orthostatic hypotension.

Distal, postganglionic, sympathetic cholinergic (sudomotor) function may be evaluated by provoking axon reflex mediated sweating. The thermoregulatory sweat test provides a non-localising measure of global pre-ganglionic and postganglionic sudomotor function.[1,11]

The particular selection of tests is dependent on the clinical presentation but may include[12]:

- FBC and differential.
- Fasting blood glucose.
- HIV testing.
- Immunoelectrophoresis of blood and urine.
- Plasma norepinephrine (supine and standing).
- Porphyria investigations.
- Genetic testing for inherited neuropathies.
- Amyloid investigation.
- Autoantibody assessment: antinuclear antibody, rheumatoid factor, anti-Ro/SS-A, anti-La/SS-B, antibodies to acetylcholine receptor, paraneoplastic antibodies-anti-Hu (type 1 anti-neuronal nuclear antibody (ANNA-1), Purkinje-cell cytoplasmic antibodies type 2 (PCA-2), collapsin response-mediator protein 5 (CRMP-5)). See also the separate article on Plasma Autoantibodies.
- ECG:
  - Variation in heart rate with respiration of fewer than 10 beats per minute is abnormal
  - Measure beat to beat variation of R-R interval (with respiration and during Valsalva manoeuvre)
- Nerve conduction studies (often normal, as affected fibres are small and not assessed by this or electromyogram (EMG) studies).
- Cystometry (bladder pressures).
- CSF examination (lumbar puncture):
  - Protein changes with dorsal root ganglia damage
  - Changes of HIV or AIDS
  - Changes consistent with paraneoplastic neuropathies (not specific)
- Imaging studies:
  - Barium swallow
  - Urodynamic studies (ultrasound may be employed)
  - Positron emission tomography (PET) scanning for cardiac sympathetic dysfunction (diabetes)
- Vascular studies:
  - Doppler studies
  - Infrared thermometry
  - Skin blood flow measures (transcutaneous oxygenation, skin temperature)
- Some more specific tests that have been suggested:
  - Sympathetic skin responses (using EMG equipment)
  - Quantitative sensory testing (comparison of sensory thresholds)
  - Thermoregulatory sweat test
  - Quantitative sudomotor axon reflex test (tests thermoregulatory pathways)

Associated diseases
There is a variety of diseases associated with autonomic neuropathy. This can be appreciated from the causal conditions listed above.
Management

Management should start from initial diagnosis and incorporate patient education about the condition and implications for the patient. This may range from measures to prevent orthostatic hypotension to improvements in self-care (from hygiene to care of diabetes mellitus).

- Treatment of the underlying cause.
- Orthostatic hypotension: see also the separate article on Hypotension.
- Gastrointestinal dysfunction:
  - Gastroparesis in patients with diabetic autonomic neuropathy is improved by rigorous control of blood glucose concentrations. [19]
  - Eat small meals and eat often.
  - Lower the fat content of the diet.
  - Prokinetic agents for gastroparesis can be used (metoclopramide, domperidone and erythromycin). A jejunostomy tube may rarely be required.
  - Bowel hypomotility. This can be helped with:
    - Increased dietary fibre and an increase in fluid intake.
    - Use of stool softeners and/or an osmotic laxative.
    - Trying out a gluten-free diet and restriction of lactose.
    - Colestyramine, clonidine, somatostatin analogues, pancreatic enzyme supplements, and even antibiotics (such as metronidazole), which have been tried. [4]

- Genital autonomic neuropathy:
  - Treatment of erectile dysfunction.
  - Vaginal lubricants and oestrogen creams may help.

- Autonomic dysfunction of the urinary tract:
  - Timed voiding schedules and bladder contractions increased by a Valsalva manoeuvre.
  - Clean intermittent self-catheterisation.
  - Cholinergic agonists (eg bethanechol) have a limited role.

- Hyperhidrosis:
  - See also the separate article on Hyperhidrosis.

Complications

Many complications exist. The most severe are:

- Cardiac arrest, cardiac dysrhythmias, sudden cardiac death [4, 14]
- Blood pressure fluctuations and the risk of cerebral and cardiac ischaemia.

Prognosis

The prognosis is determined by the particular cause of the autonomic neuropathy. In most cases the course is one of gradual progression. In the case of diabetes mellitus the prognosis is improved with good control of diabetes. Other measures to halt progression may be applicable, such as abstinence from alcohol or by treatment of correctable syndromes.

Further reading & references
