Approach to a Case of Autonomic Peripheral Neuropathy

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Abstract

Autonomic neuropathy is the term used to describe autonomic disturbances resulting from diseases of the peripheral autonomic nervous system. This is a group of disorders in which the small, lightly myelinated and unmyelinated autonomic nerve fibers are selectively targeted. Most often, autonomic neuropathies occur in conjunction with a somatic neuropathy (i.e. with motor weakness and/or sensory loss), but they can occur in isolation. Causes of autonomic neuropathies are immune-mediated, paraneoplastic, infectious, toxic and drug-induced, hereditary, nutritional and idiopathic. Amongst all, diabetes mellitus is the most common cause. Autonomic features, which involve the cardiovascular, gastrointestinal, urogenital, sudomotor, and pupillomotor systems, occur in varying combination in these disorders. Orthostatic hypotension is often the first recognized and most disabling symptom. Noninvasive, well-validated clinical tests of autonomic functions along with a host of laboratory tests are of immense value to diagnose the presence and to demonstrate the distribution of autonomic failure. Treatment aims to treat specific cause of the autonomic neuropathy (if possible) and to control symptoms of autonomic dysfunction. Present review attempts to outline clinical approach to a case of autonomic peripheral neuropathy.

What are The Causes of Autonomic Peripheral Neuropathy?

Various causes of autonomic neuropathies are enumerated in Table 1. Diabetes mellitus is the most common cause of autonomic neuropathy.

How do Autonomic Neuropathy Manifest Clinically?

The autonomic nervous system (ANS) modulates numerous body functions, and therefore, dysfunction of this system can manifest with numerous clinical phenotypes. Most often, they occur in conjunction with a somatic neuropathy (i.e. with motor weakness and/or sensory loss) as in Gullain-Barre syndrome (GBS), but they can occur in isolation (as in pandysautonomia).

Various autonomic abnormalities seen in a case of autonomic neuropathy are as follows:

- **Cardiovascular:**
  - Orthostatic hypotension (OH)- symptoms of orthostatic giddiness. May be associated with palpitations, nausea, pallor or tremulousness. In severe cases, episodes of syncope can occur after standing up from supine position.
  - Labile hypertension
  - Brady and tachyarrhythmias- may present with palpitations or syncope

- **Gastrointestinal:**
  - Dysphagia, constipation, episodic diarrhoea,
fetal incontinence, gastroparesis (cause persistent fullness and subsequent abdominal pain and vomiting), early satiety, bloating

○ Urogenital:
  • Urinary retention or incontinence, bladder urgency, bladder frequency, nocturia, enuresis, incomplete bladder voiding, impotence, loss of ejaculation, retrograde ejaculation, vaginal dryness

○ Thermoregulatory:
  • Hypothermia, hyperpyrexia

○ Secretomotor:
  • Anhidrosis or hypohydrosis (mainly in feet), hyperhidrosis (in feet/hands/head), gustatory sweating, dryness of mouth/eyes, excessive salivation

○ Pupillomotor:
  • Abnormalities of size (presents with blurred vision, glare in bright sunlight, difficulty in focusing, poor night vision)

○ Skin and joints:
  • Feeling of coldness, acrocyanosis, pallor, mottling or redness (vasomotor changes)
  • Loss of hair, nail thickening/discholoration
  • Charcot’s joints: misshaped, crepitus, excessive range of movement, pain

In general, some symptoms, such as those of orthostatic intolerance, are common in autonomic neuropathies, whereas other symptoms, such as complete anhidrosis, are rare as primary manifestation. OH is often the first recognized symptom and typically is the most disabling.

Most autonomic neuropathies have symptoms of sympathetic as well as parasympathetic dysfunction. However, some neuropathies may have only sympathetic (pure adrenergic neuropathy) or parasympathetic (pure cholinergic neuropathies like chronic idiopathic anhidrosis and Lambert-Eaton myasthenic syndrome (LEMS)) dysfunction.

Many hereditary autonomic neuropathies, neuropathies seen in connective tissue diseases, leprosy, acquired immunodeficiency syndrome (AIDS), diphtheria, lyme disease, uremia, chronic inflammatory demyelinating neuropathy (CIDP) and alcoholic neuropathies have mild autonomic dysfunction, which is usually clinically unimportant. While in neuropathies associated with diabetes, amyloidosis and in chronic paraneoplastic autonomic neuropathies, autonomic involvement is severe and clinically important.

Most autonomic neuropathies are chronic in nature and have insidious onset of symptoms. Some neuropathies, like acute pandysautonomia, GBS, botulism, porphyria, drug-induced and toxic autonomic neuropathies, have acute to subacute onset of the symptoms.

Detailed family history may yield information about possible inherited forms of autonomic neuropathy. In some cases, involvement may be subtle in certain family members, thus escaping detection.

**WHAT ARE THE SALIENT FEATURES OF VARIOUS AUTONOMIC NEUROPATHIES?**

**Diabetic autonomic neuropathy**: It typically presents late in the course of diabetes and is generally accompanied by other features of distal sensorimotor polyneuropathy. There is an increase in overall mortality and sudden death in patients with diabetic autonomic neuropathy. Erectile failure is present in 30-75% of diabetic men and can be the earliest symptom of diabetic autonomic neuropathy. Constipation and diabetic neuropathy are common in autonomic neuropathies, whereas other symptoms, such as complete anhidrosis, are rare as primary manifestation. OH is often the first recognized symptom and typically is the most disabling.
gastroparesis are two important manifestations in diabetics, seen in 60%7 and 50%8 of the patients respectively.

**Acute and subacute autonomic neuropathies:** Autonomic dysfunction of various degrees has been reported in 65% of patients of GBS admitted to the hospital.9 Serious cardiac arrhythmias tend to be more frequent in GBS patients with severe quadriparesis and respiratory failure.10

Acute pandysautonomia is characterized by the rapid onset of combined sympathetic and parasympathetic failure without somatic and motor involvement, although reflexes are usually lost during the course of the illness. About half of the patients have autonomic signs to ganglionic acetylcholine receptors, which may play a pathogenetic role.10 Only 40% of the patients recover fully to premorbid status.2 Like GBS, this illness may present as post/parainfectious event3 and these patients may have mild sensory-motor signs and cytoalbuminological dissociation in cerebrospinal fluid.11 Because of these similarities, acute and subacute pandysautonomias are sometimes considered as GBS variants.11 Acute dysautonomias can be restricted to the cholinergic system (acute cholinergic neuropathy).3

Dysautonomia is common in acute intermittent porphyria, and autonomic overactivity predominates over autonomic failure, although both are present and often coexistent.3

Botulism presents with the acute development of cholinergic failure, ptosis, ophthalmoplegia, bulbar weakness, and generalized neuromuscular paralysis.1 Dilated pupils, with poor response to light and accommodation, are characteristic autonomic signs. The illness begins with gastrointestinal manifestations.2 Typically, the symptoms begin 12-36 hours after the ingestion of home-canned food contaminated by Clostridium botulinum.3

**Hereditary autonomic neuropathies:** Hereditary sensory autonomic neuropathy (HSAN) is a group of neuropathies characterized by prominent sensory loss with autonomic features but without significant motor involvement. Currently, these neuropathies are divided into five main groups (HSAN I-V). HSAN is distinctly rare. Sensory loss in HSAN predisposes to unnoticed, recurrent trauma that may lead to neuropathic joints, nonhealing ulcers, infections, and acral mutilations. Out of five types, HSAN I is the only autosomal dominant disorder and it is the most common familial sensory neuropathy.10 Autonomic manifestations are most prominent in type III HSAN (Riley-Day syndrome or familial dysautonomia). The axon-reflex mediated, vasomotor response (the flare) after intradermal histamine is absent in all HSAN.12

Fabry’s disease is an X-linked recessive disorder. It is characterized by severe, paroxysmal pains in the hands and feet, a truncal reddish-purple maculopapular rash, and angiectases of the skin and mucous membrane, together with the painful distal peripheral neuropathy, progressive renal disease, corneal opacities, and cerebrovascular accidents.2,10 Autonomic manifestations include decreased sweat, saliva and tear production, impaired cutaneous flare response, and disordered intestinal motility.2

**Amyloid neuropathy:** Autonomic dysfunction commonly accompanies the polyneuropathy of both primary (AL; associated with immunoglobulin light chains) and hereditary (familial amyloid polyneuropathy, autosomal dominant) amyloidosis. These patients have other systemic features including hepatomegaly, macroglossia, cutaneous ecchymosis, cardiomyopathy, and nephrotic-range proteinuria.2,10

**Paraneoplastic autonomic neuropathies:** This occurs frequently in association with anti-Hu antibodies. These antibodies are commonly found in patients with small-cell lung carcinoma, but can also occur in non-small-cell lung carcinoma and malignancies of gastrointestinal tract, prostate, breast, prostate, bladder, kidney, pancreas, testis, and ovary. Autonomic neuropathy can be the sole manifestation of an anti-Hu related paraneoplastic disorder or part of general paraneoplastic syndrome.12,14 Autoantibodies specific for neuronal nicotinic acetylcholine receptors in the autonomic ganglia also have been found in patients with paraneoplastic autonomic neuropathy.10 Malignancies associated with these antibodies include small-cell lung carcinoma, thymoma, bladder carcinoma, and rectal carcinoma.2

LEMS is an acquired presynaptic disorder of neuromuscular transmission that cause weakness similar to that of myasthenia gravis, cranial nerve abnormalities, depressed or absent reflexes, and autonomic changes like dry mouth and eyes, impotence, constipation, and bladder symptoms. Abnormalities are predominantly restricted to parasympathetic nervous system. Majority of the cases are paraneoplastic.15,16

**Miscellaneous:** Acute, subacute and chronic autonomic dysfunctions can occur in settings of connective tissue diseases including systemic lupus erythematosus, scleroderma, mixed connective tissue disease and especially, Sjögren syndrome.2,3

In leprous neuropathy, focal anhydrosis occurs in association with impaired pain and temperature perception in the cooler parts of the body. These symptoms are the earliest neurological manifestations of leprosy.17

Of all cytotoxic agents, clinically evident dysautonomia occurs most consistently with vincristine. The abnormalities generally reverse several months after the drug is stopped.18

Postural orthostatic tachycardia syndrome (POTS) is characterized by symptomatic orthostatic intolerance (not OH) and an increase in heart rate to >120/min or
by 30/min with standing, most commonly in young adult women.¹

**WHAT ARE THE IMPORTANT POINTS/TESTS FOR CLINICAL EXAMINATION OF AUTONOMIC NEUROPATHY?**

Examination of skin, mucous membrane, nails and joints may indicate presence of autonomic dysfunction. Careful general examination may also give clue to the etiology. For example, characteristic skin changes are observed in leprosy and angiookeratoma of the trunk is suggestive of Fabry’s disease. Occurrence of arthritis and rash can suggest a connective tissue disorder. Pupillary examination may reveal Argyll-Robertson pupil, Horner’s syndrome or tonic pupils. Detailed neurological evaluation with special emphasis on motor and sensory system examination is important to detect associated somatic peripheral neuropathy. Presence of pyramidal, extrapyramidal, or cerebellar signs indicate a separate neurological disorder of the autonomic nervous system like multisystem atrophy or Parkinson’s disease.

Noninvasive, well-validated clinical tests of autonomic functions are very useful and widely used. These tests are of immense value to diagnose the presence and to demonstrate the distribution of autonomic failure.¹⁹ These tests are summarized in Table 2.

A combination of these tests is usually required because certain ones are sensitive to sympathetic dysfunction and others to parasympathetic dysfunction.²⁰ No food, coffee, or nicotine is permitted for 3 hours before the tests. Medications affecting ANS are stopped for five half-lives.¹⁹

Measurement of lying, sitting and orthostatic blood pressure to detect a postural decrease is one of the simplest bedside clinical tests of autonomic function. Sustained drops in systolic (>20 mm Hg) or diastolic (>10 mm Hg) BP after standing for at least 2 min that are not associated with an increase in pulse rate of >15 beats per minute suggest autonomic deficit. In nonneurogenic cause of OH (e.g. hypovolemia), the BP drop is accompanied by a compensatory increase in heart rate of >15 beats per minute.¹³ Cold pressure test and isometric exercise test have not been well validated clinically.²⁰

Electrocardiography can be used to monitor heart rate while examiner observes respiratory rhythm to determine if normal respiratory variations are present. Beat-to-beat BP and pulse monitoring is required to record changes in these parameters during Valsalva maneuver. Sympathetic skin response (SSR) can be done in electrophysiology laboratory. Special laboratory equipments are required for thermoregulatory sweat test.

### Table 2: Autonomic function testing²¹,²²

<table>
<thead>
<tr>
<th>Tests</th>
<th>Normal Response</th>
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<tbody>
<tr>
<td><strong>Tests for cardiac parasympathetic nervous system function</strong></td>
<td></td>
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<tr>
<td>1. Heart rate variability with deep respiration (respiratory sinus arrhythmia)</td>
<td>1. Maximum minus minimum heart rate &gt;/= 15 beats/min; E/I ratio 1.2 (age-dependent)</td>
</tr>
<tr>
<td>2. Heart rate response to Valsalva maneuver</td>
<td>2. Valsalva ratio &gt;/= 1.4</td>
</tr>
<tr>
<td>3. Heart rate response to standing</td>
<td>3. Increase 11-90 beats/min; 30:15 ratio &gt;/=1.04</td>
</tr>
<tr>
<td><strong>Tests for sympathetic adrenergic function</strong></td>
<td></td>
</tr>
<tr>
<td>1. Blood pressure response to upright posture</td>
<td>1. Fall in BP &lt;/= 30/15 mm Hg</td>
</tr>
<tr>
<td>2. Blood pressure response to Valsalva maneuver</td>
<td>2. Phase1- BP rise, phase 2- gradual reduction to plateau, phase 3- fall, phase 4- overshoot</td>
</tr>
<tr>
<td>3. Cold pressor test</td>
<td>3. Rise in BP by 15-20/10-15 mmHg</td>
</tr>
<tr>
<td>4. Isometric exercise test</td>
<td>4. Rise in systolic-diastolic BP &gt;/= 15 mmHg</td>
</tr>
<tr>
<td><strong>Tests for sympathetic cholinergic function</strong></td>
<td></td>
</tr>
<tr>
<td>1. Thermoregulatory sweat testing (TST)</td>
<td>1. Normal pattern of colour change of the indicator over all body and limbs</td>
</tr>
<tr>
<td>2. Quantitative sudomotor axon reflex test (QSART)</td>
<td>2. Pattern of normal sweating over all body and limbs</td>
</tr>
<tr>
<td>4. Sweat imprint methods</td>
<td>4. Normal sweating all over body and limbs</td>
</tr>
<tr>
<td><strong>Tests for lacrimal function</strong></td>
<td></td>
</tr>
<tr>
<td>1. Schirmer’s test</td>
<td>1. Length of moistened area 11-15 mm</td>
</tr>
<tr>
<td><strong>Pressor infusion test</strong></td>
<td></td>
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<tr>
<td>1. Blood pressure response to infusion of noradrenaline</td>
<td>1. Rise in BP and slowing of heart rate</td>
</tr>
<tr>
<td>2. Blood pressure response to infusion of angiotensin II</td>
<td>2. Rise in BP and slowing of heart rate</td>
</tr>
<tr>
<td>3. Heart rate response to atropine and neostigmine</td>
<td>3. Rise in BP and slowing of heart rate</td>
</tr>
<tr>
<td><strong>Cutaneous flare response</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cutaneous flare response to intracutaneous histamine or skin scratch</td>
<td>1. One cm wheal after 5-10 minutes, surrounded by red areola, which in turn surrounded by erythematous flare that extends 1-3 cm beyond the border of wheal</td>
</tr>
<tr>
<td><strong>Tests for pupillary denervation</strong></td>
<td></td>
</tr>
<tr>
<td>1. Response to instillation of topical pharmacological agents (e.g. cocaine)</td>
<td>1. Depends on agent used</td>
</tr>
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</table>
(TST) and quantitative sudomotor axon reflex test (QSART). They respectively assess capacity to produce sweat qualitatively and quantitatively. Quinirazine or Alizarine red is used as sweat indicator powder in TST.

How to Investigate a Case of Autonomic Neuropathy?

Although clinical diagnosis is essential for diagnosing autonomic neuropathies, special studies can be helpful in identifying a particular autonomic neuropathy. In most cases, the laboratory assists in identifying subclinical or subtle changes. Various tests for laboratory assessment of autonomic neuropathy are enumerated in Table 3.

In pure autonomic neuropathies, because the involved fibers are small myelinated and unmyelinated fibers, nerve conduction study can be normal. Plasma catecholamine measurements have been used as an index to separate postganglionic from preganglionic failure. In a disorder where the lesion is preganglionic, resting supine NE is normal, but the response to the standing will be reduced or absent. In a postganglionic lesion, the supine values would be reduced if the lesion is widespread. Measurements of plasma norepinephrine levels are low and do not rise on head-up tilt table testing in pandysautonomia. For evaluation of bladder dysfunction cystometrogram is required, while barium studies are useful for gastrointestinal

Table 3: Laboratory assessment of autonomic neuropathy

<table>
<thead>
<tr>
<th>Chemistry, hematology, and pathology</th>
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<tr>
<td>Complete blood count and differential</td>
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<tr>
<td>Fasting blood glucose or glucose tolerance test</td>
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<tr>
<td>HIV testing</td>
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<tr>
<td>Immunoelcctrophoresis of blood and urine</td>
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<tr>
<td>Plasma norepinephrine (supine and standing)</td>
</tr>
<tr>
<td>Porphyria investigations- urinary porphyrin concentration</td>
</tr>
<tr>
<td>Genetic testing for inherited neuropathies</td>
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<tr>
<td>Fat aspirate, rectal biopsy, or gingival biopsy for amyloid</td>
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</table>

Autoantibody assessment

- Antinuclear antibody
- Rheumatoid factor
- Anti-Ro/SS-A, Anti-La/SS-B
- Antibodies to P/Q-type calcium channel
- Antibodies to acetylcholine receptor
- Paraneoplastic antibodies- anti-Hu, Purkinje-cell cytoplasmic antibodies type 2 etc.

Electrophysiological studies

- Nerve conduction studies (including repetitive stimulation)
- Quantitative sensory testing

Table 4: Symptomatic treatment of autonomic neuropathies

<table>
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<tr>
<th>Orthostatic hypotension</th>
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<tr>
<td>- Plenty of fluids (up to 10 L/day)</td>
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<tr>
<td>- Adequate salt intake (up to 10 g/day)</td>
</tr>
<tr>
<td>- Mineralocorticoid: 9α-fludrohydrocortisone (0.1-0.3 mg/day)</td>
</tr>
<tr>
<td>- α-receptor agonist: Midodrine (2.5 mg to 10 mg tds)</td>
</tr>
</tbody>
</table>

Gastrointestinal dysfunction

- Gastroparesis:
  - Control of blood sugars
  - Low fat content of diet
  - Prokinetics: Metochlopramide (10 mg p.o. 30 mins before meals)
    - Domperidone (10-20 mg qds)
    - Erythromycin (250 mg tds)
  - Bowel Hypomotility:
    - Increased intake of high fiber diet with plenty of fluids
    - Stool softeners and osmotic laxative
  - Bowel hypermotility:
    - Restriction of lactose and gluten
    - Cholestyramine, clonidine, somatostatin analogue, metronidazole

Genital dysfunction

- Erectile failure:
  - PDE 5 inhibitors: Sildenafil (50 mg), Tadafil (20 mg) etc.
    - Caution: ischemic heart disease, hypotension, significant OH, concomitant nitrates
  - Intracorporal injection of vasoactive substances e.g. papavarine and PGE
  - Transurethral delivery of vasoactive agents
  - Mechanical devices e.g. vacuum erection device, constricting rings
  - Penile prosthetic implants
  - Vaginal lubricants & estrogen creams

Urinary tract dysfunction

- Timed voiding schedules
- Bladder contraction increased by Crede maneuver
- Clean intermittent self catheterization (For impaired detrusor activity)
- Cholinergic agents: Bethanechol (10-30 mg tds) in detrusor areflexia
- Anticholinergic agents: Tolterodine tartrate (2 mg bid) for overactive bladder

Labile hypertension

- Beta-blockers (propranolol)

Tachyarrhythmias

- Anticholinergic Agents: trihexyphenidyl, glycopyrrolate
dysfunction. Nocturnal penile tumescence can be recorded in sleep laboratory.

How to Treat a Patient with Autonomic Neuropathy?

Treatment aims to treat specific cause of the autonomic neuropathy (if possible) and to control symptoms of autonomic dysfunction. Adequate control of blood sugar is very important in diabetic neuropathy. Steroids and intravenous immunoglobulins are helpful in immune-mediated neuropathies. Immediate withdrawal of offending drug or toxin is necessary. As most of the autonomic neuropathies are not completely reversible, symptomatic management holds very important place in these cases. It is summarized in Table 4.

REFERENCES


Announcement

XVII Annual Conference of Association of Physician of India Assam Chapter APICON Assam 2006 will be held at Tezpur from 15th to 17th December 2006.

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