Clinical Summary

Pure autonomic failure

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ICD codes
ICD-9:
Hypotension: 458

ICD-10:
Hypotension: 195

OMIM
Hypotension, orthostatic: 146500

Synonyms
Bradbury-Eggleston syndrome; Bradbury Eggleston syndrome; Pure progressive autonomic failure; Idiopathic orthostatic hypotension

Historical note and nomenclature

In 1898, Langley coined the term "autonomic nervous system." He identified the enteric, sympathetic, and parasympathetic components. Cannon later added an adrenal-hormonal component in the early 20th century.

It was in 1925 that Samuel Bradbury and Cary Eggleston first described the entity now known as pure autonomic failure, which encompasses the failure of both the sympathetic and the parasympathetic nervous systems (Bradbury 1925). Initially, these 2 clinicians described 3 patients with idiopathic orthostatic hypotension, which is the key characteristic of this uncommon disease. The nomenclature evolved from idiopathic orthostatic hypotension (Bradbury-Eggleston syndrome) into pure progressive autonomic failure and finally to the generally accepted term, pure autonomic failure. The name pure autonomic failure was introduced by Oppenheimer as one of the primary chronic autonomic failure syndromes in addition to Parkinson disease with autonomic failure and multiple system atrophy.

Pure autonomic failure was defined by the 1996 Consensus Committee of the American Autonomic Society and the American Academy of Neurology to be "an idiopathic sporadic disorder characterized by orthostatic hypotension usually with evidence of more widespread autonomic failure and no other neurological features" (Consensus

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Committee of the American Autonomic Society and the American Academy of Neurology 1996).

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Clinical manifestations

The clinical features of pure autonomic failure depend on the disease time course and stage of advancement.

Table 1. Clinical Features of Pure Autonomic Failure

- Orthostatic hypotension
  - Lightheadedness
  - Postural dimming of vision
  - Syncope
  - Postural neck or head discomfort (coat-hanger pattern)
  - Postprandial orthostatic hypotension
- Postprandial angina pectoris
- Impotence
- Supine hypertension
- Anhidrosis
- Leg weakness
- Constipation or diarrhea
- Bladder and micturition dysfunction
- Mild anemia
- Fixed, constant pulse
- Dysphagia
- Nasal stuffiness
- Horner syndrome
- Pupil abnormalities
- Chronic intestinal pseudo-obstruction
- Leg restlessness

Adapted from: (Korczyn 1995).

The initial presenting symptoms may consist of vague weakness, dizziness, or male impotence. One clue to the diagnosis of autonomic failure is orthostatic hypotension that may be aggravated by a big meal (Thomaides et al 1993), prolonged standing, or standing too quickly from a sitting or supine position. Patients, especially those living in hot climates, may complain of heat intolerance and lack of sweating; excessive vasodilation may exacerbate orthostatic hypotension.

Intelligence is usually preserved but cognitive function may show decline (Heims 2006). One reported patient developed anxiety and restlessness (Cheshire 2000). There is a wide variation in pupillary findings (Bremner and Smith 2006a; 2006b). Bradbury and Eggleston reported that 2 of their 3 patients had misshapen pupils that were reactive to light (Bradbury 1925). Nasal stuffiness can be present (Korczyn 1995); but surprisingly, saliva production is normal (Jordan 1998).

Constipation is common in the early phase along with discomfort (Mabuchi 2005). Micturitional disturbances may be present, and can vary from general voiding disturbances to nocturnal urinary frequency (Sakakibara 2000).

Leg restlessness (hypotensive akathisia) appears in few patients; some may move their legs to maintain their blood pressure. Patients

have reported that the sensation of the movements stop when lying down (Cheshire 2000).

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Clinical vignette

No information was provided by the author.

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Etiology

The current literature suggests that the accumulation of alpha-synuclein in the affected parts of the autonomic nervous system plays a major role in pathogenesis.

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Pathogenesis and pathophysiology

Alpha-synuclein is a protein consisting of 140 amino acids with a molecular weight of 14 kDa (Dev 2003), and is expressed in high levels in many nervous tissues (Papachroni 2005).

The following mechanisms are postulated functions of alpha-synuclein: (1) inhibition of phospholipase D2, which is involved in signal induction (Spillantini and Goedert 2000); and (2) inhibition of nuclear histone acetylation promoting neurotoxicity (Kontopoulos et al 2006). However, the exact mechanisms still must be elucidated.

In Parkinson disease it is hypothesized that the pathogenesis may be as follows: studies in tissue culture have shown that alpha-synuclein activates surrounding microglia. This process of activation accelerates dopaminergic degeneration. The microglial activation along with the proinflammatory mediators leads to nigral neurodegeneration (Zhang et al 2005).

It is possible that reactive microglia could induce oxidative stress in dopaminergic neurons and that such oxidative stress may finally lead to nitration of alpha-synuclein and death of dopaminergic neurons in Parkinson disease (Shavali et al 2006).

Alpha-synuclein is a defining protein for a Lewy body, which is the pathological hallmark of Parkinson disease. The Lewy bodies found in pure autonomic failure patients are indistinguishable from the ones found in Parkinson disease patients (Shibao et al 2005). Lewy bodies have a dense eosinophilic core and pale halo along with various amounts of iron, hyperphosphorylated microfilaments, lipids, protein, ubiquitin, and alpha-synuclein (Matsuzaki et al 2004).

Lewy bodies are found in different parts of the nervous system of patients with pure autonomic failure, including the myenteric plexus neurons of the esophagus, small intestine, and smooth muscle of the rectal wall. They are also found in adrenomedullary cells and the smooth muscle of the bladder (Arai et al 2000). The parasympathetic and the sympathetic neurons are equally affected (Arai et al 2000). The postganglionic components are more severely affected than preganglionic components. Cell loss is noted in the intermediolateral columns and sympathetic ganglia (Low 1997). A study conducted by Akimitsu and colleagues showed reduced unmyelinated fibers and collagen pockets in sural nerve biopsies (Akimitsu et al 1993).

The pathophysiological basis of the clinical spectrum is best explained by the degeneration of respective parts of the autonomic nervous system. Pure autonomic failure is also one of a continuum of alpha-

synucleinopathies that includes Parkinson disease and diffuse Lewy body dementia (Hague et al 1997; Kaufmann et al 2001).

Central nervous system. Neurogenic orthostatic hypotension occurs due to extensive loss of sympathetic innervation (Kaufmann et al 2004). This process leads to postural dizziness, dimming vision, neck or head discomfort (coat hanger headache), and syncope due to cerebral hypoperfusion (Korczyn 1995; Mathias et al 1999). Cerebral hypoperfusion has also been cited for the cognitive decline (Heims 2006).

Cardiovascular system. With time, the body partially adapts to the frequent hypotension so there is compensatory hypertension when the patient is supine, which is caused by an increase in systemic vascular resistance (Kronenberg 1990; Shannon et al 2000). The fixed pulse rate is explained by parasympathetic failure (Mathias 2003).

Genitourinary. Patients have low bladder compliance attributed to the preganglionic neuropathology in the pelvic nerves. The postganglionic lesion leads to denervation hypersensitivity. The pudendal nerve can also be affected but EMG evidence of denervation in the external sphincter is more characteristic of multiple system atrophy. Detrusor hyperreflexia indicates supranuclear parasympathetic lesions (Mitsui 1993). Lewy bodies are also found in the bladder (Sakakibara 2000).

Gastrointestinal. The exact mechanisms that produce gastrointestinal disturbances in pure autonomic failure are poorly understood but disruption of local neuronal circuits and the enteric nervous system are suspected. Impaired gastric emptying is reported, and in 1 case chronic intestinal pseudo-obstruction developed (Yamanaka 2006). Constipation is a much more common problem for patients (Mabuchi 2005). Dysphagic symptoms could be due to the accumulation of alpha-synuclein in the myenteric plexus in the esophagus (Arai et al 2000).

Hematological. Reduced sympathetic stimulation leads to mild anemia that further complicates orthostatic hypotension. The sympathetic system acting through beta-2 adrenergic receptors modulates erythropoiesis through increased erythropoietin production. Direct measurements of the erythrocyte mass and total blood volume showed decreases in hemoglobin due to decreased erythropoietin production (Robertson and Krantz 1994; Robertson 2004). Treating the anemia also increases standing blood pressure values.

Muscular. Leg restlessness has been reported as a problem (Cheshire 2000), but the pathophysiology remains a mystery (Allen 2004).

Dermatological. Sweating dysfunction can be seen as a general lack of sweating (Hague 1997; Nakazato 2004).

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Epidemiology

In 1 study, the age of onset varied from 51 to 80 years with a mean of 67 years (Cohen 1987).

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Prevention

There are no means of prevention reported in literature.

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Differential diagnosis

The differential diagnosis for pure autonomic failure includes: multiple system atrophy, Parkinson disease with autonomic failure, autoimmune autonomic neuropathy, paraneoplastic autonomic neuropathy, diabetic autonomic neuropathy, and amyloidotic autonomic neuropathy.

The 1996 American Academy of Neurology Consensus Statement defined multiple system atrophy as "a sporadic progressive adult onset disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination" (Consensus Committee of the American Autonomic Society and the American Academy of Neurology 1996).

Patients with multiple system atrophy who present with only autonomic and urinary dysfunction can be incorrectly diagnosed with pure autonomic failure, so it is important to wait 5 years before diagnosing pure autonomic failure (Bannister 1983). In multiple system atrophy, the dysfunction of parasympathetic and sympathetic systems is central in location, but in pure autonomic failure the impairment is peripheral. The progression of multiple system atrophy is faster than that of pure autonomic failure, and the prognosis is poorer. Early in the disease process, the distinction may be difficult, but distinguishing findings are usually evident during follow-up. It is imperative to take a proper history and physical examination.

There are some features, depending on the time of onset, that can help determine multiple system atrophy from pure autonomic failure. If stridor develops along with sleep abnormalities then it is most likely multiple system atrophy. Anhidrosis will present earlier in pure autonomic failure along with faintness. Urinary disturbances come about earlier in multiple system atrophy as compared to pure autonomic failure (Mabuchi 2005).

There are neuropharmacological tests that can help differentiate multiple system atrophy from pure autonomic failure (Low 1997; Robertson 2004): (1) blood pressure response to oral water intake is increased in multiple system atrophy, but variable in pure autonomic failure. (2) Blood pressure response to ganglionic blockade in multiple system atrophy is decreased greatly, but in pure autonomic failure there is just a modest decrease. (3) Baroreceptor mediated vasopressin release in preserved in patients with pure autonomic failure but blunted in patients with multiple system atrophy. (4) Plasma supine norepinephrine level is generally normal in multiple system atrophy and reduced in pure autonomic failure. (5) Low plasma norepinephrine levels usually indicate pure autonomic failure. (6) Growth hormone release with clonidine injection is absent in multiple system atrophy, signaling an abnormal hypothalamic-pituitary pathway, whereas in pure autonomic failure there is an increase of growth hormone indicating that the hypothalamic-pituitary axis is intact.

Imaging can also help differentiate the 2 disorders. Multiple system atrophy has brainstem or cerebellar atrophy, with T2 hyperintensity of the pons (the hot-crossed bun sign), which is not present in pure autonomic failure (Watanabe 2002).

Cardiac PET scans differentiate the 2 diseases based on uptake of 6-[18F]-fluorodopamine, which demonstrates cardiac innervation by the postganglionic sympathetic neurons. The findings indicate that in pure autonomic failure the uptake is decreased or lost and in multiple system atrophy it is normal (Goldstein et al 2002). Interestingly, similar findings are seen in Parkinson disease patients with autonomic failure

and to a lesser degree in Parkinson disease patients without clearly evidenced dysautonomia. Control scans with 13N-ammonia uptake are normal in all 3 groups. This finding further supports the link between these disorders demonstrating Lewy bodies.

With SPECT scintigraphy there is decreased uptake of 123I-metaiodobenzylguanidine on the myocardial scintigrams in pure autonomic failure (Yoshida 1997).

Sphincter EMG results are frequently abnormal in multiple system atrophy and normal in pure autonomic failure.

Early in the disease process, testing with QSART is normal in multiple system atrophy, but becomes abnormal as the disease advances because of transsynaptic defect. QSART is usually abnormal in pure autonomic failure (Low 1997).

Neuropathological involvement in multiple system atrophy is in the preganglionic and the central nervous systems. In pure autonomic failure there is predominately postganglionic pathology with a loss of ganglionic neurons (Akimitsu 1993; Arai et al 2000). Patients with multiple system atrophy have characteristic glial cytoplasmic inclusions; in pure autonomic failure there are Lewy bodies (Robertson 2004).

The 1996 American Academy of Neurology Consensus Statement states that, "A minority of patients with PD defined by the United Kingdom Parkinson's disease Brain Bank criteria may also develop autonomic failure, including orthostatic hypotension" (Consensus Committee of the American Autonomic Society and the American Academy of Neurology 1996). Clinical features of Parkinson disease with autonomic failure include parkinsonism, including rigidity, bradykinesia, tremor, and truncal instability; cerebellar dysfunction that includes ataxia, maintaining balance, and coordination; and difficulty with speech.

Clinical features that may help in the differential diagnosis of pure autonomic failure versus autoimmune autonomic neuropathy are abnormal deep tendon reflexes (Inoue 1989) and complaints of a dry mouth (Low 1997). Patients should be asked about sensory loss or neuropathic pain. The history should also include a recent viral infection or surgical procedure. A family history of autoimmune disorders may suggest autoimmune autonomic failure (Robertson 2004).

Paraneoplastic autonomic dysfunction can demonstrate similar features to pure autonomic failure, so a careful history is warranted. A complete blood work-up should be done, along with a paraneoplastic panel. The neoplasm in such patients is most likely be a small cell lung carcinoma (Robertson 2004; Weimer 2005). A variety of antibodies are associated with this syndrome including ANNA-1 (HU), ganglionic acetylcholine receptor, CV-2, and several others.

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Diagnostic workup

Pure autonomic failure is a diagnosis of exclusion. A complete history and thorough physical examination are essential. Most advocate waiting at least 5 years after symptom onset before giving the final diagnosis to ensure that no nonautonomic systems become involved. Parkinson disease with autonomic failure, multiple system atrophy, and severe autonomic neuropathy are the most common considerations and each have characteristic symptoms and signs.

One of the most important factors to determine orthostatic hypotension is the simple measurement of blood pressure. Blood

pressure should be noted in the supine and the standing positions, throughout the day, at least 3 times. Orthostatic hypotension is defined by a systolic blood pressure drop of at least 20 mm Hg and a diastolic drop of at least 10 mm Hg following position changes (these must happen within 3 minutes of standing) (Robertson 2004). Some require a 30 mm Hg drop in systolic blood pressure to increase specificity. Symptoms produced should also be noted.

A patient who is suspected to have pure autonomic failure should have standardized autonomic reflex screening tests consisting of sudomotor, cardiovagal, and cardioadrenergic testing in a standardized lab, if available.

The following are reported findings in pure autonomic failure but are not necessarily specific for this entity: (a) there is no overshoot of the blood pressure during phase 4 Valsalva maneuver testing during continuous blood pressure monitoring (Jordan 1998; Vogel 2005); (b) sinus arrhythmia is decreased (Jordan 1998); (c) abnormal quantitative sudomotor axon reflex testing (QSART); (d) abnormal beat-to-beat blood pressure response to Valsalva maneuver; and (e) orthostatic hypotension on head-up tilt with inadequate heart rate response.

Neuropharmacological test findings include: a reduced plasma supine norepinephrine level, low baseline plasma norepinephrine levels, intact growth hormone response to clonidine, and an increase in plasma arginine vasopressin in response to head-up tilt testing (Jordan 1998; Robertson 2004; Mabuchi 2005).

Cardiac PET shows decreased 6-[18F]-fluorodopamine uptake indicating cardiac denervation (Goldstein et al 1997; 2002). SPECT scintigraphy reveals decreased uptake of 123I-MIBG on the myocardial scintigrams in pure autonomic failure (Yoshida et al 1997).

Neuropathological findings include the presence of alpha-synuclein and Lewy bodies (Robertson 2004).

Sphincter EMG is usually normal.

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Prognosis and complications

Pure autonomic failure is a chronic, slowly degenerative condition. The disease progresses insidiously but slowly. This pattern is attributed to the body's compensatory mechanisms and slow neurodegeneration (Mabuchi 2005). The overall prognosis for patients with pure autonomic failure is good, even though there is ongoing disease progression. The major complications arise from symptomatic orthostatic hypotension. Bladder catheterization may be required in severe cases and associated complications must be kept in mind. There is also a possibility of life threatening cardiac arrhythmias, so caution is warranted (Yoshida 1997).

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Management

Pure autonomic failure requires a careful communicative relationship with the patient, patient's family, and other care providers. A special session or sessions may be needed to educate the patient and all parties involved in the patients care. Patients living in hot climates, especially older patients, need to be warned against dehydration and the effects of vasodilation. Sexual dysfunction may produce marital or relationship challenges and counseling should be offered if needed. Patients should be cautioned against alcohol use that may cause

vasodilation and reduce orthostatic tolerance. Always offer emotional and supportive care and consultation to social workers if necessary. A more comprehensive approach to the management of autonomic failure can be found in the MedLink clinical summary, Treatment of autonomic neuropathy.

Currently, there is no specific preventative treatment of pure autonomic failure, but symptomatic treatment is beneficial. There are 2 categories of treatment for orthostatic hypotension (usually the main clinical feature of pure autonomic failure): nonpharmacological and pharmacological.

The following nonpharmacological maneuvers have been advised to help orthostatic hypotension: leg crossing, squatting, pressure stockings, swimming, bed elevation, and isotonic exercise (Weimer 2005). In addition, 16 oz of water may help keep the blood pressured raised.

Pharmacological treatments include: (1) fludrocortisone, a mineralocorticoid, through its mineralocorticoid activity increases intravascular volume (0.05 to 0.20 mg/day); (2) midodrine, an alpha-adrenergic agonist, constricts arterioles and decreases venous pooling via reducing venous capacitance (2.5 to 10 mg 3 times during the day) (Gilden 1993). The best time to take the last dose would be no later than 5 PM, because of possible supine hypertension and insomnia. Scalp itching is a common and expected physiologic side effect and is not a sign of an allergic response (Robertson 2004).

Numerous other second-line medications are used.

Possible future management options include plasma exchange, which may be an option for some patients. A plasma exchange clinical trial sponsored by the National Institute of Neurological Disorders and Stroke is currently recruiting patients.

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Pregnancy

Use caution when prescribing medications because of possible side effects.

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Anesthesia

Patients with pure autonomic failure require careful monitoring due to blood pressure changes (Low 1997).

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Associated disorders

Parkinson disease with autonomic failure
Multiple system atrophy
Autoimmune autonomic neuropathy
Idiopathic autoimmune neuropathy
Lewy body dementia
Paraneoplastic autonomic disorder

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Related summaries

Autonomic dysfunction in sleep disorders
Horner syndrome
Treatment of autonomic neuropathy

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Differential diagnosis

multiple system atrophy
Parkinson disease with autonomic failure
autoimmune autonomic neuropathy
paraneoplastic autonomic neuropathy
diabetic autonomic neuropathy
amyloidotic autonomic neuropathy

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Demographics

For more specific demographic information, see the Epidemiology, Etiology, and Pathogenesis and pathophysiology sections of this clinical summary.

Age
19-44 years
45-64 years
65+ years

Population
None selectively affected.

Occupation
None selectively affected.

Sex
male>female, >1:1

Family history
family history may be obtained

Heredity
heredity may be a factor

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