

Shy-Drager Syndrome: Recognition And Management

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Shy-Drager syndrome is an uncommon disorder in which the patient experiences progressive autonomic failure. It is a multisystem degenerative disease that involves the central autonomic, cerebellar, basal ganglia, pyramidal, or spinal motor neurons. The mean age of onset is 55 years. A male predominance is noted, with a 2 or 3:1 ratio. About 11 percent of patients with orthostatic hypotension have Shy-Drager syndrome. The disease is progressive, and patients die 7 to 20 years after the onset of neurologic symptoms. The syndrome was first noted in 1925, when Bradbury and Eggleston¹ published a paper on 3 patients with postural hypotension and unchanging pulse rate. Shy and Drager² provided the first comprehensive clinical and pathologic details of central nervous system involvement in this disorder.

We report 1 patient with cholinergic dysfunction and orthostatic hypotension. The diagnosis of this rare neurological disease in our patient was made through a work-up in a geriatric assessment unit.

Case Report

A 65-year-old woman was seen in our geriatric assessment clinic on 31 October 1989. She was a registered nurse who retired because of progressive gait and incontinence problems of about 2 years' duration.

The patient had been admitted to a local hospital on 2 April 1989 with acute urinary retention, urinary tract infection, and ataxia. It was noted then that the patient had both stress and urge incontinence with the likely diagnosis of neurogenic bladder. Her condition had been treated previously with urethral dilatation, bethanechol, and nitrofurantoin, with no apparent improvement, so the patient discontinued the treatment on 31 March 1989. The patient had

been using a straight urinary catheter six times daily since that hospitalization.

In the interview she said that during the last 2 years she had progressive difficulty in walking, with a tendency to fall to the left side. This unsteadiness of gait had led to three falls, none with loss of consciousness. She described the episode of falling as loss of balance while standing but denied any actual vertigo, weakness, nausea, vomiting, tinnitus, or headache. It was because of her falls and frequent incontinence that she insisted on retiring from a nursing career of 20 years. She also had been feeling light-headed on standing and used a cane intermittently. Her daughter noted deterioration in her mother's handwriting and that buttoning was becoming more a difficult task. The patient denied dysphagia, bowel problems, or sleep disturbances. She had a weight loss of 60 pounds during the previous 3 years, thought to be secondary to a stressful situation at home.

She had had a tonsillectomy in 1940. Thrombocytopenia and anemia were diagnosed in 1976 as a consequence of hypothyroidism, and she had been prescribed levothyroxine since 1976. She had a history of a positive tuberculin test (PPD) for which she was prescribed isoniazid and pyridoxine for 1 year in 1980. Her family history included a benign thyroid tumor and kidney stones in the daughter, heart disease in both her father and mother, and colon cancer in an aunt. There was no history of neurological disorders. Her current medications were amitriptyline 25 mg daily at bedtime and levothyroxine 0.15 mg daily.

Three weeks before her initial clinic visit, the patient was brought to Arizona from Iowa by her daughter, who was living in Tucson. The patient's youngest daughter and her grandchildren had moved in with her in Iowa, and according to her local daughter, there was considerable familial upset and strife during these past several years that contributed to the patient's not doing well. Before her youngest daughter and grandchildren moved in, the patient had lived alone since her husband's suicide in 1965. The patient's own mother was in a nursing home in Sioux City,

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Iowa, and the patient was seeing her mother frequently and was helping in her care.

The patient was alert and oriented but had minor difficulties remembering the particulars of specific events. She was somewhat slow in responding to questions, but her answers were invariably accurate, as verified by her daughter. Her blood pressure was 150/90 mmHg supine but dropped to 90 systolic after 1 minute and 60 systolic after 5 minutes in the standing position. The patient became markedly dizzy and felt as though she was going to faint. No increase in pulse rate was noted. Her pulse rate was 70 beats per minute and regular with no beat-to-beat variability, and no murmur was heard.

Her neurological examination showed that cranial nerves II through XII were intact. A motor examination of both upper and lower extremities failed to elicit any evidence of focal motor deficit to active or resistance testing. Deep tendon reflexes were diminished on the left ankle. There was no Babinski reflex, no tremor, no masked facies, and no monotonous voice or cogwheel rigidity; her skin and oral mucosa were slightly dry. Pinprick sensation appeared to be intact. Vibration was diminished in the lower extremities and upper extremities.

On gait testing, the patient's gait was unsteady when she was not using a cane, and she tended to veer and fall toward her left, which was accentuated on turning. There was a positive Romberg sign toward the left. The patient was able with concentration to perform rapid alternating movement and heel-shin-toe maneuvers successfully, although somewhat less accurately and slower than normal. She also had a mild dysmetria during a finger-to-nose maneuver (worse with the left hand). The patient fell backward when she closed her eyes, but there was no drift. Her gait was slow and careful, and she had difficulty turning but did not shuffle. She felt lightheaded when asked to look up while standing and when asked to look over her head while supine. Pressure on each carotid artery separately did not reproduce the symptom of lightheadedness. The fundi were normal, and extraocular muscles were intact with no nystagmus. Visual field testing was normal to confrontation. The Folstein Mini-Mental State examination score was 30/30, consistent with normal cognition,³ and the results of the Geriatric Depression Scale⁴ were normal. Find-

ings from the rest of her general examination were normal.

Differential Diagnosis

Possible diagnoses initially entertained were midline cerebellar tumor versus hydrocephalus (obstructive versus normal pressure), chronic subdural hematoma, and Shy-Drager syndrome. Laboratory evaluation included a complete blood count, urinalysis, automated sequential analysis (SMA-20), erythrocyte sedimentation rate, serologic test for syphilis, serum B₁₂ and folate measurements, fasting blood glucose test, and cholesterol profile, in addition to nerve conduction studies and thyroxine, thyroid-stimulating hormone levels. The only positive findings were a triglyceride value of 110 mg/dL and a cholesterol value of 158 mg/dL. A computed tomogram of the brain (with and without contrast media) showed a larger left ventricle without signs of obstruction and a probable small colloid cyst in the area of the third ventricle. An intravenous pyelogram showed probable cystitis and mild blunting of the calyces, possibly secondary to reflux. Findings on a routine chest radiograph were consistent with chronic obstructive pulmonary disease. The laboratory data were otherwise normal.

A diagnosis of Shy-Drager syndrome was made, and the patient was educated about the disease. She was instructed to avoid activities that promote venous pooling and encouraged to do mild exercise, especially swimming. She was instructed to drink more coffee, especially after a meal, and was advised to sit on the side of the bed for several minutes before getting up in the morning. It was also suggested that she sleep with the head of her bed elevated 8 to 12 inches. She was prescribed fludrocortisone, 0.05 mg twice daily, which improved the symptoms of orthostatic hypotension. Further improvement was achieved when the dose was increased to 0.1 mg twice daily. A higher dose was attempted, but the patient developed numerous marked side effects at that level, so the dose was reduced to the previous level.

Discussion

The manifestation and the neurologic findings in Shy-Drager syndrome are summarized in Tables 1 and 2. The major manifestation is autonomic insufficiency with wide swings in blood pressure

Table 1. Neurologic Findings in the Shy-Drager Syndrome.

System	Manifestations
Autonomic	
Visual	Visual dimness, Horner's syndrome, iris atrophy, anisocoria, decreased lacrimation, corneal insensitivity, impaired eye movement, nystagmus
Genital	Impotence, loss of libido
Urinary	Nocturnal diuresis, incontinence, retention
Cardiovascular	Dizziness, syncope, orthostatic hypotension
Temperature regulation	Heat intolerance, sweat disturbances
Gastrointestinal	Constipation, diarrhea, incontinence
Somatic	
Corticospinal and corticobulbar	Dysarthria, hyperreflexia, Babinski sign
Cerebellum	Ataxia of gait, intention tremor
Basal ganglia	Resting tremors, rigidity, masked facies
Anterior horn cells and neuromuscular junction	Muscle atrophy and fasciculation

but no changes in pulse rate. Patients complain of dizziness, syncope, or lightheadedness on standing; postexertional weakness; and unsteadiness of gait. Central neuron degeneration is manifested by parkinsonian features, intention tremor, ataxia, dysarthria, and in some cases, corticobulbar and corticospinal tract signs. Intellectual and emotional functions are preserved until late in the course of the disease. Laboratory studies are usually normal, although some nonspecific electroencephalogram abnormalities have been reported. An electromyogram might show involvement of anterior horn cells.

There are a number of simple tests that can be used to screen for autonomic dysfunction. One is the response of blood pressure and heart rate to assuming the upright posture. Another simple test is the diastolic pressure overshoot following the Valsalva maneuver. A simple test is the hand-grip test with measurement of heart rate and blood pressure. An inspection of the electrocardiogram for respiratory arrhythmia can also provide useful clues.

Autonomic dysfunction in the Shy-Drager syndrome is an example of multiple system atrophy and is attributed to efferent adrenergic failure in

the central nervous system.^{1,5} Cholinergic insufficiency also occurs, which causes abnormalities in vagal,^{6,7} ocular,⁸ bladder,² and sweat gland⁹ functions. In the patient described here, urinary tract symptoms were prominent and preceded other symptoms. She refused to use medication for urinary tract symptoms after failing to benefit from low doses of bethanechol. Many patients with Shy-Drager syndrome have a transurethral resection without benefit.¹⁰ More useful medications, such as bethanechol chloride, selectively stimulate muscarinic receptors.^{11,12} Subcutaneous administration of bethanechol chloride has not only relieved urinary and bowel dysfunction but also activated secretions by all glands, suggesting hypersensitive responses of the end organs.¹³

Attempts to treat the cerebellar ataxia have so far proved fruitless. There has been some success with some drugs, including 5-hydroxytryptophan, isoniazid, baclofen, and propranolol. Apparent temporary exacerbations of ataxia have resulted from cigarette smoking.¹³ A severe reduction in the level of noradrenaline in the central nervous system also occurs in both Parkinson disease and multiple system atrophy, but thus far trials using drugs known to enhance or antagonize noradrenaline seem to be without substantial effect in either disorder.¹⁴

Treatment of postural hypotension is fraught with difficulties. Principles of management include the following: First, it is important to be concerned about a low standing blood pressure if the patient has symptoms. Studies of patients with autonomic failure and multiple system atrophy have found that autoregulation was preserved at a systolic blood pressure approaching 60 mmHg, which is well below the 80 mmHg at which auto-

Table 2. Manifestations of the Shy-Drager Syndrome in Approximate Descending Order of Frequency.

Orthostatic hypotension
Impotence (male)
Pyramidal signs
Sweating abnormalities
Extrapyramidal signs
Bladder dysfunction
Cerebellar signs
Dysarthria
Gastrointestinal dysfunction
Others

regulation fails in normal persons.^{15,16} Second, patients have a tendency to develop recumbent hypertension. Third, the long-term adjustment to postural hypotension is through control of blood volume, determined by antidiuretic hormone and the renin-angiotensin-aldosterone mechanism.

Several factors can lower blood pressure and thus enhance postural hypotension. Straining, for example, might result in a Valsalva maneuver with substantial reduction in blood pressure. The supine blood pressure in patients with autonomic failure is lowest in the morning and rises gradually during the day. Patients exposed to high temperatures tend to have more symptoms. Substantial postprandial hypotension occurs soon after food ingestion and can last for up to 3 hours after a standard meal. Drugs with vasoactive properties, even if only a minor action of the agent, can result in serious vascular changes because of hypersensitivity.

Treatment usually follows one of two courses: either to reduce the vascular volume into which pooling occurs on standing, or to increase the volume of blood available for pooling. Classically, treatment involves pharmacologic and nonpharmacologic approaches (Table 3). A variety of drugs have been used to raise standing blood pressure. The sites of action include blood vessels by means of vasoconstriction and prevention of vasodilatation, the heart, and the kidney, in addition to plasma volume expansion. Drugs acting as vasoconstrictors can be broadly divided as follows:

1. Directly acting agents. A variety of agents that act directly on adrenoreceptors with partial success have been reported to be of benefit¹⁷ including phenylephrine and midodrine. These agents can, however, cause severe vasoconstriction in peripheral vessels.
2. Indirectly acting agents. Ephedrine and tyramine might have a role in patients with incomplete lesions¹⁸ as could clonidine, which has actions both centrally and peripherally.¹⁹

Additional drugs include dihydroergotamine, which is predominantly a vasoconstrictor with a long history in treatment of postural hypotension.²⁰ Drugs that have been used on the assumption that blood pressure control can be improved by preventing vasodilatory mechanisms include

Table 3. Treatment Modalities for Orthostatic Hypotension.

Modalities	Detail Descriptions
Disease specific	Eradicate conditions that favor pooling of blood and impede venous returns Correct electrolyte disturbance and volume depletion Eliminate hypotension-inducing drugs Treat adrenal insufficiency, hypothyroidism, anemia, and other treatable diseases
Other	
Mechanical	Head-up position of bed Elasticized body garment Mild exercise if tolerated
Plasma and extracellular fluid volume expanders	High-salt diet Fludrocortisone
Vasoconstrictor	Ephedrine Vasopressin Amphetamine Methylphenidate Monoamine oxidase inhibitors with amphetamine
Other drugs	Indomethacin Propranolol Midodrine (investigational) Dihydroergotamine

β -adrenoceptor blockades, prostaglandin synthetase inhibitors, and dopamine antagonists. Propranolol at doses of 40 to 240 mg daily can be helpful.²¹ Some drugs that prevent postprandial hypotension include caffeine²² and somatostatin analogs.²³ Two cups of coffee could provide sufficient caffeine to help reduce postprandial hypotension.

Drugs acting on the heart can improve postural hypotension. Several authors report benefits from using pindolol.^{24,25} Improvement could be due to an improved cardiac output. Two other β -blockers with α -adrenergic partial agonist, prenaloter²⁵ and xamoterol,²⁶ have been used with good results. Unlike pindolol, no cardiac failure has been reported with these drugs.

The most widely used treatment modality is plasma volume expansion. Fludrocortisone is the most important drug used.²⁷ In an initial dose of 0.1 mg daily, it increases effective vasoconstriction on standing by augmenting the action of noradrenaline released by normal sympathetic efferent activity; however, it can aggravate recumbent

hypertension. In higher doses it can expand the blood volume, improve cardiac output, and therefore reduce postural hypotension. In the elderly, however, it can lead to heart failure or cause rebound hypertension, as occurred with our patient. Desmopressin is a vasopressin-like agent that has antidiuretic effects. Administered intramuscularly, desmopressin prevents nocturnal polyuria and overnight weight loss and raises the supine blood pressure in the morning.²⁸ Studies with intranasal desmopressin indicate that it is equally effective; its major limiting side effect is hyponatremia.

Supportive measures include telling patients to sleep with a head-up tilt at night in an attempt to increase the patient's blood volume²⁹ by reducing renal arterial pressure and promoting renin release and thus increasing blood volume.²⁷ A temporary measure after a patient has been recumbent for a few days is the use of a custom-fitted elastic counterpressure garment.³⁰ These measures were attempted in the patient described here with partial improvement of her symptoms.

The use of a cardiac pacemaker can be useful to elevate heart rate during postural change.³¹ Benefit has occurred in patients who apparently have had an incomplete autonomic lesion. A pacemaker can also prevent excessive bradycardia in response to elevation of blood pressure by drugs. In the future there is hope for the development of a device that is closely linked to blood pressure control and that can administer short-acting drugs, such as noradrenaline, when needed.³²

Conclusion

Despite the rarity of this condition, it is important to consider this diagnosis in the differential diagnosis of idiopathic orthostatic hypotension.

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