Case 9
Shy-Drager Syndrome: Central Autonomic Failure

Ben Garcia was a 54-year-old executive with a large, thriving investment company. He was well regarded among his clients as the consummate professional. He and his wife of 32 years had two children, both of whom were college graduates. Life was great until Mr. Garcia found, to his embarrassment, that he was occasionally impotent. His wife teased him gently about “getting old.” However, his impotence rapidly progressed from “occasional” to “frequent” to “every time.” Additionally, Mr. Garcia was experiencing urinary problems. He felt enormous urgency to urinate, but had difficulty producing a urinary stream. His embarrassment (because of the nature of his symptoms), combined with his busy schedule, kept him from seeking medical attention. It wasn’t until he arose from bed one morning and fainted that he made an appointment with his physician. By the time he saw his physician, he had been feeling dizzy every morning for a month and had an array of symptoms that convinced him that something was terribly wrong. In addition to impotence, urinary difficulties, and dizziness when he stood up, he had double vision, indigestion, diarrhea, and heat intolerance.

Mr. Garcia was referred to a neurologist who, based on the global nature of his symptoms and the results of a specific ocular test, diagnosed him as having Shy-Drager syndrome, a rare, progressive disease of the central autonomic nervous system. Shy-Drager syndrome is associated with degeneration of preganglionic neurons of the intermediolateral cell column of the spinal cord, autonomic ganglia in the periphery, and autonomic centers in the hypothalamus. As a result, both the sympathetic and parasympathetic divisions of the autonomic nervous system are profoundly impaired.

As part of his treatment, Mr. Garcia was instructed to elevate his head during sleep and to wear support stockings to prevent blood from pooling in his veins. He also took an aldosterone analogue to increase his blood volume. Each of these measures was an attempt to ameliorate the dizziness and fainting that he experienced when he stood up. Mr. Garcia and his family understood that the treatments were palliative and that there was no cure for his degenerative disease. He died at home at 58 years of age, 4 years after the onset of his symptoms.

Q QUESTIONS

1. Which organ systems or bodily functions would you expect to be adversely affected by degeneration of the central autonomic nervous system?

2. As experienced by Mr. Garcia, often the earliest symptom of Shy-Drager syndrome is impotence. Describe the normal autonomic control of male sexual response, and explain why it is impaired in patients who have central autonomic failure.

3. Describe the autonomic control of micturition, including the functions of the detrusor muscle and the sphincters of the bladder. Why did Mr. Garcia experience urinary urgency, but was then unable to void normally?

4. Why was Mr. Garcia heat-intolerant?

5. The ocular test involved instilling methacholine (a cholinergic muscarinic agonist) into the conjunctival sac. In Mr. Garcia, methacholine caused exaggerated miosis (constriction of the pupil caused by contraction of the circular muscle of the iris). Is there a plausible explanation for why his response to methacholine was greater than that of a healthy person?
6. The hallmark of Shy-Drager syndrome is orthostatic hypotension (a decrease in blood pressure that occurs when a person stands up). When a healthy person stands up, orthostatic hypotension does not occur because autonomic reflexes operate to maintain a constant arterial pressure. What are the reflex responses that prevent orthostatic hypotension in healthy individuals, and why were these responses impaired in Mr. Garcia?

7. Support stockings prevent blood from pooling in the leg veins. How would these stockings have been helpful in alleviating Mr. Garcia’s orthostatic hypotension?

8. Aldosterone and its analogues produce an increase in extracellular fluid volume. How did the aldosterone analogue help to alleviate Mr. Garcia’s orthostatic hypotension?

9. Name three classes of drugs that would have been absolutely contraindicated in Mr. Garcia’s case.
1. The autonomic nervous system controls the function of virtually every organ system and every bodily function, usually as a result of an interplay between the sympathetic and parasympathetic divisions. (See Table 1–5 in Case 8 to review autonomic control of organ system functions.) Central failure of the autonomic nervous system, as seen in Shy-Drager syndrome, would be predicted to adversely affect every organ system. This failure affects control of arterial blood pressure; function of the bronchioles, which regulate the flow of air into the lungs; motility, secretion, digestive, and absorptive functions of the gastrointestinal tract; filling and emptying of the bladder; male sexual response, including erection and ejaculation; function of the eye muscles that control near and far vision; activity of the sweat glands involved in thermoregulation; and metabolic functions of the liver and adipose tissue. It is difficult to imagine a more comprehensive list of bodily functions, and it is easy to appreciate why Mr. Garcia was so sick.

2. The male sexual response consists of erection and ejaculation. Erection is under parasympathetic control (muscarinic receptors), which causes the venous sinuses of the corpus cavernosa to fill with blood and the penis to become erect. Ejaculation is under sympathetic control (α receptors), which causes the ischiocavernosa and bulbocavernosa muscles to contract.

3. The detrusor muscle of the bladder wall is composed of smooth muscle that has both sympathetic (β receptors) and parasympathetic (muscarinic receptors) innervation. The internal sphincter of the bladder is also composed of smooth muscle, with both sympathetic (α receptors) and parasympathetic (muscarinic receptors) innervation. The external sphincter is skeletal muscle, which is under trained voluntary control.

Normal bladder function has two phases: filling and emptying (micturition). When the bladder is filling with urine, sympathetic control dominates. The detrusor muscle relaxes (sympathetic β2 receptors), and the internal sphincter contracts (sympathetic α1 receptors). When the bladder is full, mechanoreceptors in the wall sense the fullness and relay this information to the spinal cord and then to the brain stem, where the micturition reflex is coordinated. During micturition, or emptying, parasympathetic control dominates. The detrusor muscle contracts (parasympathetic muscarinic receptors), and the internal sphincter relaxes (parasympathetic muscarinic receptors), allowing the bladder to empty.

In Mr. Garcia, both sympathetic control (filling) and parasympathetic control (emptying) of the bladder were impaired. Because of the loss of sympathetic control, his bladder did not fill normally, and he felt urinary urgency when his bladder contained a small amount of urine. Because of the loss of parasympathetic control, his bladder could not contract forcefully enough to produce a normal urinary stream.

4. Thermoregulatory sweat glands are controlled by the sympathetic nervous system. This sympathetic innervation is unusual in that postganglionic neurons innervating the sweat glands release acetylcholine (i.e., they are sympathetic cholinergic fibers). [In contrast, most sympathetic postganglionic neurons release norepinephrine (i.e., they are sympathetic adrenergic fibers).] In keeping with this unusual feature, the receptors on sweat glands are the cholinergic muscarinic type. As the name suggests, thermoregulatory sweating is important for dissipation of the heat generated by metabolism, especially when the ambient temperature is high. Loss of sympathetic innervation in Shy-Drager syndrome led to impairment of thermoregulatory sweating and caused heat intolerance.

5. The ocular test involved instilling a cholinergic muscarinic agonist into the eye. In healthy persons, the cholinergic agonist methacholine produces miosis (constriction of the pupil) by causing the circular muscle of the iris to contract. In Mr. Garcia, the miosis response was exaggerated. Why would he have an exaggerated parasympathetic cholinergic response when his central parasympathetic nervous system was impaired? The answer involves the sensitivity of cholinergic receptors on the circular muscle of the iris. Without normal parasympathetic innervation, the
receptors are up-regulated (i.e., increased number of receptors), a condition called denervation hypersensitivity. Thus, when an exogenous cholinergic agonist (e.g., methacholine) was instilled in Mr. Garcia's eyes, it caused a larger than usual miosis response.

6. When a healthy person stands up suddenly, blood pools in the veins of the legs, and there is a transient decrease in arterial blood pressure. This decrease is only transient because it is detected and immediately corrected by reflexes involving the sympathetic and parasympathetic nervous systems (baroreceptor reflex). For this reflex to occur, information about blood pressure must be relayed from baroreceptors in the carotid sinus to specific brain stem centers. These brain stem centers orchestrate an increase in sympathetic outflow to the heart and blood vessels and a decrease in parasympathetic outflow to the heart (Figure 1-13). The sympathetic and parasympathetic effects include an increase in heart rate and contractility, which combine to produce an increase in cardiac output; constriction of arterioles, with a resultant increase in total peripheral resistance; and venoconstriction, which increases venous return to the heart. These effects, in combination, restore arterial pressure to its normal set-point value. The responses occur so quickly that healthy persons are unaware of them, or may be briefly aware of an increase in heart rate.

![Diagram](diagram.png)

**Figure 1-13** Responses of the baroreceptor reflex to a decrease in mean arterial pressure. $P_a$, arterial pressure; TPR, total peripheral resistance.

In Mr. Garcia, the baroreceptor reflex was severely impaired because of central damage to the sympathetic and parasympathetic nervous systems. When he stood up, his arterial pressure fell (orthostatic hypotension) and could not be corrected by autonomic reflexes. He felt dizzy and fainted because the sustained decrease in arterial pressure caused a decrease in cerebral blood flow.

7. Support stockings constrict the veins in the legs and prevent the venous pooling of blood that initiates an orthostatic decrease in blood pressure.

8. Aldosterone and its analogues increase the reabsorption of Na$^+$ in the kidney and thereby increase both extracellular fluid volume and blood volume. Because most of the blood volume is contained in the veins, an increase in total blood volume leads to an increase in venous blood volume and venous return, which produces an increase in cardiac output and arterial pressure.

9. Mr. Garcia's disease involved loss of both sympathetic and parasympathetic control of his organ systems. Any drug that would further antagonize either sympathetic or parasympathetic activity (e.g., inhibition of autonomic receptors on the end organs) would have exacerbated his problems.
Your list might include α-adrenergic receptor antagonists (e.g., phenoxybenzamine), β-adrenergic receptor antagonists (e.g., propranolol), muscarinic receptor antagonists (e.g., atropine), and nicotinic receptor antagonists (e.g., hexamethonium). (Recall that nicotinic receptors are present on postsynaptic neurons in both sympathetic and parasympathetic ganglia.)