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Autonomic Neuropathy: Patient Care

Preface

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Diabetic neuropathy, encompassing a wide range of abnormalities within the peripheral nervous system (PNS), is actually a number of different syndromes, each with a vast array of clinical and subclinical manifestations.[1] Given that diabetic neuropathy is a very broad and complex area, this *Diabetes Spectrum* From Research to Practice section is devoted to just a few selected issues in the area of autonomic neuropathy.

Functional Organization of Nervous Tissue

A brief review of the functional organization of nervous tissue will serve as a reminder of the complexity of this system.[2] While the brain and spinal cord constitute the central nervous system (CNS), the PNS consists of various nerve processes that connect the brain and spinal cord with receptors, muscles, and glands. The PNS is subdivided into an afferent system (sensory division), which transmits information from receptors to the CNS, and an efferent system (motor division), which conveys information from the CNS to muscles and glands.

Further subdivision of the efferent system includes the somatic and autonomic systems. While neurons of the somatic system transmit information from the CNS to

skeletal muscles, the autonomic nervous system (ANS) conveys information from the CNS to smooth muscle, cardiac muscle, and glands.

In the ANS, many organs are doubly innervated, receiving fibers from the sympathetic and parasympathetic divisions. Whereas parasympathetic nerve fibers regulate resting type functions (e.g., emptying the urinary bladder), sympathetic responses are involved in the body's preparation for physical activity (e.g., strenuous muscular work).

Prevalence of Diabetic Neuropathy

The frequency at which any form of neuropathy exists in the diabetic population varies greatly in the literature. The prevalence of the most common form of diabetic neuropathy, known as distal symmetric polyneuropathy, has been estimated with a range of 0–93%.[1,3,4] The prevalence of autonomic neuropathy, based on assessment of abnormal cardiovascular autonomic function tests, has been reported to be in the range of 8–90%.[5-7] Three major reasons explain the wide estimates of prevalence rates: *1)* different patient cohorts (e.g., type 1 or type 2; clinic- or population-based), *2)* different assessment modalities with varied sensitivity and specificity (e.g., clinical or subclinical measures), and *3)* different minimal criteria used to define the presence of neuropathy.

Assessment of Cardiovascular Autonomic Neuropathy

Reduced heart rate variability is the earliest indicator of cardiovascular autonomic neuropathy (CAN) (i.e., abnormalities of heart-rate control and vascular dynamics). Three major syndromes (cardiac denervation, exercise intolerance, and orthostatic hypotension)[8] are associated with dysfunction of the cardiovascular autonomic nervous system.

Given the prevalence of CAN and adverse clinical manifestations of this disorder (readers are referred to the articles in this issue by Schumer [p. 227], Albright [p. 231], and Gilden [p. 237]), health care providers need to be aware of the various noninvasive, bedside assessment modalities of CAN that can be performed in the office setting. Three of the most widely used tests for the determination of CAN include RR-variation during deep breathing, the Valsalva maneuver, and blood pressure response to standing.[9] According to the American Academy of Neurology, these are established tests, meaning that they are "accepted as appropriate by the practicing medical community for the given indication in the specified patient population."[10]

RR-variation during deep breathing. Determination of the amount of RR-variation (i.e., heart-rate variability) measures the magnitude of sinus arrhythmia. Normally,

during inspiration the electrocardiographic R-R interval (interval between R waves of QRS complexes) shortens, while during expiration the interval lengthens. Schumer and associates describe the performance of this test and explain the different analytical measurements that have been used for the determination of RR-variation. Although the magnitude of change in heart rate as a result of respiration is, for the most part, a function of parasympathetic activity, it has been shown that the sympathetic nervous system is also capable of affecting this variability.[11]

Valsalva maneuver. While RR-variation represents a simple neural reflex arc, the Valsalva maneuver is a much more complex reflex arc involving sympathetic and parasympathetic pathways to the heart, sympathetic pathways to the vascular tree, and baroreceptors in the chest and lungs.[9] The procedure for performing the Valsalva maneuver involves recording a continuous electrocardiogram while having the individual blow into the mouthpiece of an open manometer and maintaining a pressure of 40 mmHg for 15 seconds. Normally, during the strain, tachycardia and peripheral vasoconstriction develop; and during the release, there is bradycardia and rise in blood pressure.[1]

Blood pressure response to standing. Blood pressure response to standing up is regarded mainly as a measure of sympathetic function.[12] Although the absolute fall in blood pressure is arbitrary, orthostatic hypotension is diagnosed by a fall of >20–30 mmHg in systolic pressure13 or >10 mmHg in diastolic blood pressure,[8] usually within 2 minutes of standing.

Assessment of myocardial sympathetic innervation. Imaging of myocardial sympathetic innervation with various radiotracers [e.g., I^{123} meta-iodobenzylguanidine (MIBG)] has recently evolved as a potentially exciting new noninvasive methodology for the determination of autonomic dysfunction.[14] This technique has shown reduced uptake of MIBG in diabetic patients with autonomic neuropathy and may be a more sensitive[15] and specific indicator of abnormal innervation than the standard cardiovascular reflex testing described above. Although this modality is currently a research tool, it may be helpful in furthering our understanding of the natural history of CAN. Evidence would now suggest that there is simultaneous impairment of both sympathetic and parasympathetic pathways,[16] rather than a progressive model of parasympathetic dysfunction preceding damage of the sympathetic neurons.

Association of Mortality and CAN

The sole manifestation of asymptomatic reduced heart-rate variability does not appear to be associated with premature mortality.[17] Symptomatic autonomic

neuropathy, however, has been shown to have a poorer prognosis, revealing a 10-year mortality rate of approximately 27%.[17] Those with symptomatic autonomic neuropathy may be at a higher risk of mortality compared to patients with asymptomatic autonomic neuropathy, because they may be part of a subgroup with other complications and thus more advanced disease.[18]

Assessment of sympathovagal and blood pressure circadian rhythms can reveal individuals with diabetes to have an autonomic imbalance. Twenty-four-hour power spectral analysis of heart-rate variability, a measure of sympathetic and vagal regulation of heart rate, in diabetic individuals has shown an altered circadian rhythm of increased sympathetic activity during the night.[19] Twenty-four-hour blood pressure monitoring of diabetic patients with CAN revealed an attenuation of the nighttime fall of blood pressure.[20] These results have led investigators to suggest that an abnormal predominance of sympathetic activity with a reduced fall in blood pressure at night (favoring the development of ventricular hypertrophy) may predispose diabetic individuals to the development of a cardiac event.[21] Thus, abnormalities in the sympathovagal and blood pressure circadian rhythms could be relevant to the increased risk of mortality that is associated with CAN.[17,22]

The causative relationship between CAN and mortality, however, remains speculative and unclear. Other potential explanations for this association include, but are not limited to: prolongation of the QT interval,[23] co-existence of other diabetes complications (e.g., nephropathy),[24] interrelationships with cardiovascular risk factors (e.g., blood pressure),[24-26] and severe but asymptomatic ischemia leading to lethal arrhythmias.[27]

Potential Therapeutic Interventions for Autonomic Imbalance

Since autonomic imbalance is associated with increased risk of mortality, the question is raised as to whether there are any pharmacological or nonpharmacological interventions that can modulate autonomic tone (e.g., increase reduced vagal activity). In a double-blind, randomized, and placebo-controlled study,[28] an angiotensin-converting enzyme (ACE) inhibitor was shown to increase parasympathetic activity in diabetic individuals with CAN. Likewise, clinical trials have shown that reduced vagal activity can be increased by such nonpharmacological interventions as exercise training in nondiabetic patients who have had a myocardial infarction[29] and in insulin-requiring diabetic individuals with early CAN.[30]

Exercising With Autonomic Neuropathy

Exercise is an important modality in the multidisciplinary approach to the treatment of diabetes. But as Albright's review clearly indicates, individuals with autonomic

neuropathy need to take certain precautions with regard to exercise. Attention must be given to both the presence of CAN (e.g., heart rate is an inappropriate gauge of exercise intensity), as well as other potential manifestations of autonomic neuropathy (e.g., gastropathy) when developing an exercise prescription. Each exercise prescription must be specifically tailored for the individual patient.

With commercially available instrumentation, insurance reimbursement, and the ability to perform noninvasive assessment for CAN dysfunction in the primary care setting, as discussed by Schumer and associates, the determination of the cardiovascular autonomic status of diabetic patients would seem appropriate for a number of situations (e.g., before prescribing an exercise program[31] or before induction of anesthesia for elective surgery[32]).

Other Manifestations of Autonomic Neuropathy

Whether reduced heart-rate variability is predictive of the development of other forms of autonomic dysfunction in other organ systems remains unresolved. Some problems associated with autonomic neuropathy, such as abnormal pupillary function, where the reduction of sympathetic tone results in pupils that dilate slowly, require no specific therapy. There are, however, some important safety issues for patients with abnormal pupillary function to consider (e.g., being cautious in poorly illuminated areas). Some symptoms of autonomic neuropathy develop suddenly (e.g., gustatory sweating [abnormal production of sweat associated with eating]) with considerable variation in severity. Management of gustatory sweating is difficult. Some symptoms of autonomic neuropathy (e.g., orthostatic hypotension) can be very intermittent, with neither improvement nor deterioration seen over time.

Despite the fact that some symptoms of autonomic neuropathy may be intermittent, manifestations of this disorder are responsible for some of the most troublesome and disabling problems of diabetic neuropathy. Three particular problems associated with autonomic neuropathy (orthostatic hypotension, bladder dysfunction, and gastropathy) are reviewed in this issue (pages 237, 241, and 248, respectively). The clinical manifestations, diagnostic techniques, and issues related to management of these disorders are discussed.

Bladder dysfunction. Yerkes's comprehensive review of the neurogenic bladder and types of urinary incontinence should indicate to health care providers that bladder dysfunctions of diminished sensation and increased volume capacity may occur silently in individuals with diabetes. Thus, identification of the problem is the key step toward proper management for the reduction of increased risk of secondary complications (e.g., urinary tract infections).

Orthostatic hypotension. Gilden's discussion of orthostatic hypotension highlights important safety issues. For example, there is the potential for an individual's falling and sustaining an injury as a result of a drop in blood pressure upon standing. Patients should be cautioned to avoid standing rapidly. Other points for teaching patients include avoidance of straining at stool or when urinating, hot weather, and hot showers.[33] Activities such as taking hot showers cause peripheral vasodilatation and can result in individuals becoming symptomatic.[33] Therefore, goals aimed at controlling or avoiding symptoms of orthostatic hypotension (e.g., syncopal episodes) are important in terms of both quality of life and safety.

Gastropathy. The article by Valentine and associates includes some important questions for health care providers to ask patients that may help in the identification of individuals with gastropathy. These questions may uncover that a patient is experiencing postprandial hypoglycemia followed by a late hyperglycemic peak as a result of the discrepancy between delivery of food to the small intestine, absorption of nutrients, and onset of the action of insulin. These authors' discussion of therapeutic options for management of patients identified with gastropathy clearly indicates that management begins with nonpharmacological modalities particularly related to nutritional issues. However, pharmaceutical agents may become necessary, as gastropathy can result in vicious cycles of glycemic control problems, poor nutritional status, and advanced gastrointestinal complications.

The results of the Diabetes Control and Complications Trial clearly showed that intensive diabetes therapy retards the development of abnormal RR-variation and slows the deterioration of autonomic dysfunction over time.[34] Thus, common treatment goals for health care providers and patients with regard to all autonomic disorders should include alleviation of symptoms and enhanced glycemic control to prevent continued deterioration.

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