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Vanderbilt Autonomic Dysfunction Center

Neurally Mediated Syncope

Introduction

Syncope is a sudden and transient loss of consciousness and postural tone, usually described as “fainting” or “passing out”. It is a common problem, accounting for 3% of emergency room visits. A history of an isolated episode of syncope will be found in as many as 25% of healthy young adults, especially in settings that precipitate fear, disgust or anxiety, and if not repeated does not warrant further work-up. Repeated episodes, however, may be caused by a wide variety of medical problems, and require diagnosis and treatment. It is important to distinguish syncope from “dizziness”, which generally refers to an alteration in balance, vision, or perception of the environment, without the loss of consciousness. Causes of syncope can be differentiated into two major classifications, cardiac and noncardiac. Examples of cardiac syncope are heart rhythm disturbances or abnormalities in the structure of the heart. The list below presents a useful classification of noncardiac syncope:

- Neurologic (seizures)
- Psychiatric (conversion disorder)
- Orthostatic hypotension
  - Acute Primary
    - Acute pandysautonomia
  - Acute Secondary
    - Dehydration
    - Bed Rest
    - Drugs
  - Chronic Primary
    - Pure autonomic failure
    - Multiple system atrophy
  - Chronic Secondary
    - Diabetes
    - Amyloid
    - Paraneoplastic syndromes
    - Drugs
- Neurally Mediated (Reflex)
  - Carotid sinus hypersensitivity
  - Glossopharyngeal neuralgia and syncope
  - Visceral syncope (micturition, deglutition, gastrointestinal or bronchial trauma or distention)

- Emotional (fear, disgust, pain, anxiety) syncope
- Neurocardiogenic syncope

Neurally mediated syncope:
Neurally mediated syncope (NMS) is one of the most frequent forms of syncope. It has also been known as vasovagal syncope, neurocardiogenic syncope, common or emotional fainting, or reflex syncope. Neurally mediated syncope is characterized by peripheral vasodilation and a decrease in blood pressure, or hypotension, along with bradycardia, or a slow heart rate. This hypotension leads to loss of consciousness if sufficiently severe or to presyncope if less severe or if the patient is lying down. There is general agreement that these changes in heart rate and blood pressure are due to an increase in parasympathetic tone and concomitant inhibition of sympathetic outflow. The parasympathetic and sympathetic systems are part of the autonomic nervous system. Related terms and conditions include situational fainting such as cough, micturitional, defecation, diving, sneezing, and swallowing syncope, carotid sinus syncope (shaving syncope), and autonomic conditions including hyperadrenergic and hypoadrenergic states.

Basic Pathophysiology

Performance of vital and complex mental functions depends on adequate cerebrovascular perfusion pressure. Under normal conditions, cardiovascular reflexes, such as the baroreceptor reflex, preserve arterial blood pressure and cerebral perfusion within adequate margins. Changes in posture, physical exercise, food digestion, and mental activity are among many activities that alter cardiovascular homeostasis and require the involvement of neurocardiovascular reflex mechanisms. For instance, upon standing, the increase of gravitational forces results in regional and hemodynamic changes that include a pooling of blood in the lower extremities. After a few minutes of standing, between 500 and 800 ml of blood are trapped in the distensible veins below the level of the heart, plasma moves to the interstitial fluid and a decrease in venous return, cardiac output and blood pressure occurs. These

changes are detected by stretch or baroreceptors which relay information to the central nervous system that in turn decreases parasympathetic tone (i.e., cardiac vagal tone, tachycardia) and increases sympathetic outflow (increase in norepinephrine secretion and in peripheral resistances). These changes restore blood pressure and allow for adequate cerebral perfusion during standing. The relevance of these adaptive mechanisms can be better appreciated in subjects in whom these cardiovascular reflexes are absent or severely impaired. For instance, patients with severe autonomic failure experience severe hypotension either after assuming the upright position or after food consumption (orthostatic and postprandial hypotension, respectively). Likewise, subjects with baroreflex failure experience pronounced episodes of unopposed hypertension and tachycardia. Neurally mediated syncope may represent an intermediate functional state between those conditions, and anomalies in one or several parts of the reflex arc may result in the sudden development of this syndrome. Factors responsible for NMS are varied and not always evident.

Central NMS

Central NMS remains poorly characterized in humans. Presumably, in susceptible individuals, emotional stimulation (pain, fear, sight of blood, anxiety, etc.) can activate ill-defined areas within the central nervous system that in turn trigger sympathetic inhibition (resulting in vasodilation) and parasympathetic activation (bradycardia). From blood bank statistics, it is considered that 2 to 5% of donors experience neurally mediated syncope. It is not known what percentage of subjects experiencing central NMS would also be susceptible to postural or situational NMS, nor the incidence of syncope resulting from strong emotional stimulation in the general population.

Postural NMS

Postural NMS is much more frequent than the central type. From a referral population evaluated at the Vanderbilt Autonomic Dysfunction Center, 94% of NMS cases will fall in this category. Typically, this syncope develops while the subject is standing or walking and presumably,

gravitational forces play a pivotal role in the development of this type of syncope.

Initiating factors in postural NMS have not been entirely clarified. Early studies suggested an underlying abnormality in the peripheral veins that resulted in exaggerated orthostatic pooling during the upright position in these patients. Inferences from these studies suggest that venodilatation plays an important role by reducing cardiac filling, cardiac output, and blood pressure.

Theories of NMS

There are multiple theories related to neurally mediated syncope, including:

- **The Ventricular Theory:** The concept of relative circulating hypovolemia causing venous pooling and decreased filling return to the heart is one main postulate of the "ventricular theory" of NMS. This theory suggests that when sensor mechanisms detect a decrease in cardiac output and blood pressure, a reflex increase in efferent sympathetic activity develops. The increase in sympathetic tone attempts to enhance total peripheral resistances and produces positive chronotropic (tachycardia) and inotropic (force of contraction) effects in the heart. The presence of increased cardiac sympathetic stimulation in a setting of ventricular hypovolemia is believed to result in large pressure transients evoked by contraction of the ventricular muscle on an empty chamber.
- **Baroreflex Dysfunction Theory:** Several authors have advocated defective baroreflex function as a potential mechanism accounting for the development of postural NMS. Under normal conditions, sudden changes in blood pressure affect the activity of baroreceptors located in different hemodynamic areas including the aortic arch, carotid sinus, lungs, and heart. Information from the baroreceptors is relayed to the central nervous system through the glossopharyngeal and vagus nerves. Fibers from these nerves terminate, within the central nervous system, in the nucleus of the solitary tract. In this nucleus, neuronal cell groups regulate reflex

cardiovascular activity through changes in sympathetic and parasympathetic tone. The integrated function of baroreceptors, central brain nuclei, and systemic effectors evokes cardiovascular changes, which are referred to as the baroreflex. Based upon different experimental findings, authors have proposed that decreased function of arterial baroreceptors, augmented or altered sensitivity of cardiopulmonary receptors, or sudden central resetting of baroreflexes contributes to the development of NMS. Baroreflex dysfunction is a suitable hypothesis explaining findings such as the inability of many patients with postural NMS to increase their sympathetic tone in response to orthostatic stress, the subtle, but consistent progressive hypotension during tilt, and the similarities in the efferent response with carotid sinus syncope.

- **Reduced Blood Volume Theory:** Some authors have proposed that a reduced blood volume is present in subjects susceptible to NMS. Overall, it seems that blood volume redistribution, rather than total blood volume, is more critical for the development of NMS.
- **Neurohumoral Theories:** Besides the rapid neural-cardiovascular response to changes in gravitational forces, other important adaptive processes include mid- and long-term regulatory mechanisms of blood volume control. These are typically characterized by the synthesis and release to the central or peripheral circulation of neurohumoral agents able to influence vascular and autonomic function. In this context, some authors have proposed that inappropriate secretion of some catecholamines, particularly epinephrine, or of renin, endogenous opioid peptides, vasopressin, serotonin, or endothelin may contribute to the pathogenesis of NMS.
- **Active Vasodilation Theory:** The profound hypotension observed in NMS was thought to be related to profound vasodilation in skeletal muscle resulting from cholinergic stimulation. In humans, some reports indicated sympathetic cholinergic cutaneous and skeletal muscle vasodilation in response to mental stress or isometric exercise. However, all the available recordings of muscle sympathetic nerve activity have shown

disappearance of neural traffic preceding hypotension, which makes it unlikely that an active sympathetic-cholinergic mechanism results in vasodilation. Furthermore, cholinergic blockade in individuals susceptible to NMS failed to prevent the hypotension. Overall, more experimental evidence is needed to support the involvement of vasodilation in NMS.

- **Respiration Theory:** Little attention has been paid to the changes in respiratory pattern preceding NMS and whether these changes offer insight regarding the pathophysiology of this syndrome. Frequently, patients developing NMS develop symptoms such as yawning and hyperventilation. Respiratory changes may influence the autonomic regulation of blood pressure or heart rate and under some conditions these can trigger or aggravate hemodynamic instability.
- **Cerebral Blood Flow Dysregulation Theory:** More than 35 years ago, some authors indicated that patients with NMS exhibit an abnormal cerebral vascular response to orthostatic stress. They postulated that cerebral ischemia in areas regulating cardiovascular function could initiate NMS. Results of some studies raise the possibility that abnormalities within the CNS, either functional or structural, play a pivotal role in the pathogenesis of NMS. Clearly, additional research is needed to support this possibility.

Not only is more clinical research needed to better delineate the mechanisms responsible for this syndrome, but this research has to be performed in actual subjects with NMS. It will not be surprising if what we now call NMS is ultimately recognized as the final clinical expression of multiple different conditions which are still poorly characterized.

Diagnosis of NMS

The evaluation of a patient with syncope first involves excluding other disorders of consciousness (e.g. dizziness, vertigo, seizures, coma) then determining the cause for the syncope episode. Given the many possible causes of syncopal symptoms and the unpredictable nature

(i.e., severity, timing, frequency) of syncopal events, this goal may be difficult to achieve.

In addition to characterizing the episode of loss of consciousness, an important initial objective in every case is differentiating those individuals with normal cardiovascular status from those with evident cardiac or cardiovascular disease. To accomplish these goals, the first step is to record a comprehensive medical history with particular emphasis on the description of the syncopal event, past history, family history and concomitant drug treatment.

The clinical history and physical is the most important component of the evaluation of a patient with syncope. Among cases in which a diagnosis can be made, the history and physical identify the cause in approximately 45% of cases. In an additional 8% of cases, the history and physical provide suggestive findings that are confirmed later on subsequent testing. The key points of the history should include the situation in which the event occurred, prodromal symptoms, witnessed appearance, postevent residua, past history and family history. Some causes of syncope have specific clinical presentations, such as syncope during arm exercise.

The physical examination should start with vital signs, including an assessment of orthostatic vitals. Orthostatic hypotension is defined as a fall in systolic blood pressure of at least 20 mmHg. Measuring the blood pressure on standing several times during a 3-minute period usually is sufficient to elicit this finding. Other important features of the physical examination include neurologic findings such as diplopia, dysarthria, nystagmus, ataxia and pupillary asymmetry, as well as cardiac findings such as carotid bruit, jugular venous distension, rales, a systolic murmur (of hypertrophic cardiomyopathy or aortic stenosis), pericardial rub or unequal blood pressure in the two arms.

The function of the autonomic nervous system can be determined by simple physiological and pharmacological tests. All these tests should be performed in a quiet environment after 15 minutes in the supine posture with blood pressure and heart rate monitoring.

Tilt table testing is a standard diagnostic test for

evaluating patients with syncope. It is considered the gold standard for providing diagnostic evidence indicating susceptibility to neurally mediated syncope. Several observations suggest that symptomatic hypotension-bradycardia associated with a positive head-up tilt test is comparable to the spontaneous neurally mediated syncope. Unfortunately, tilt table testing is plagued by both false-positive and false-negative tests. Thus the tests MUST be interpreted carefully and within the clinical context.

Treatment of NMS

In many cases, patient education and counseling to avoid factors that might trigger a syncopal episode (e.g. heat, dehydration, postexertional standing) is sufficient to prevent recurrence.

The initial treatment for neurally mediated syncope is often an increase in dietary salt intake, an increase in fluid consumption and discontinuation of medications that potentiate vasodilation.

Nonpharmacologic therapies include sleeping with the head of the bed raised about 6 to 12 inches and elastic support hose (at least 30 to 40 mmHg ankle counterpressure). Although effective, the hose are difficult to put on and can be quite uncomfortable in hot climates. Biofeedback has proved useful in selected patients. Mild aerobic reconditioning is an important part of therapy, often best done using water activities. In some patients, building lower extremity strength and tilt training (spending progressively longer periods of time upright) can be helpful.

Pharmacotherapy in combination with education is often necessary. The medical treatment of neurally mediated syncope is complicated by the nearly complete lack of placebo controlled trials. The best method for assessing treatment is to evaluate the patient's recurrence of symptoms and quality of life over time. The assessment of treatment efficacy must also include a careful evaluation of treatment side effects. Agents that have been used include beta-blockers, fludrocortisone, SSRIs, midodrine, disopyramide and yohimbine.

Driving Issues Related to Syncope

Patients with mild neurally mediated syncope have no restrictions on driving private vehicles and should have a 1 month event-free period before driving commercial vehicles. Mild neurally mediated syncope is characterized by mild symptoms (usually without syncope), occurs with warning, usually occurs only with standing, and occurs infrequently.

Severe neurally mediated syncope is characterized by severe symptoms (usually syncope), occurs without warning, occurs in any position, has no clear precipitating causes or occurs frequently. These patients are allowed to drive private vehicles after 3 months of documented control of the condition and commercial vehicles after they have been symptom free for 6 months.

Untreated patients with severe neurally mediated syncope are completely prohibited from driving.