Treatment

Renal Involvement due to Deranged Calcium Metabolism

Hypercalcemia of sarcoidosis warrants aggressive therapy to avoid serious renal damage. Avoidance of excessive exposure to sunlight, restriction of calcium-containing foods, and vitamin D are the principal preventive measures. Corticosteroids (0.3 to 0.5 mg/kg/day) are the most effective agents to control hypercalcemia and renal failure induced by granulomatous inflammation.[14] It has been argued that in cases where hypercalciuria is a predominant problem, corticosteroids should not be given because of their hypercalciuric effect.[15] In such a situation low-calcium diet, sodium phytate, sodium phosphate, or cellulose phosphate may be preferable. We have, however, successfully treated such patients with corticosteroids. Furthermore, chloroquine is now demonstrated to be an effective agent in the treatment hypercalcemia due to sarcoidosis.[16] In some patients high-dose steroid therapy (prednisone 1 mg/kg of body weight per day) may be required. The maximum improvement in glomerular filtration rate determines the point at which tapering of the dose should be initiated. Rapid reduction of the dose may result in a relapse. Most patients need a maintenance dose of (0.1 to 0.3 mg/kg of body weight per alternate day). In some patients a decline in renal function with hyaline glomerulofibrosis may continue despite the repeated course of corticosteroid therapy.[17,18]

Glomerulonephritis

Glomerulonephritis is a rare complication in patients with sarcoidosis and the experience with its treatment is limited. It is recommended that the patients with membranous glomerulonephropathy who excrete 2 g of protein in 24 hours or are nephrotic without significant renal impairment should be given prednisone 2 mg/kg of body weight per alternate day for eight weeks. Then the dose should be tapered over a period of four to six weeks before it is discontinued. There is little experience with use of immunosuppressive agents (cyclophosphamide, azathioprine, or chlorambucil) in this condition.

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Hyperventilation Syndrome—Hiding Behind Pseudonyms?

The hyperventilation syndrome is usually easily recognized when it follows an acute and typical form. It is often overlooked, however, when it presents in unusual ways or follows a chronic and insidious course.[1-5]

The major clinical manifestations of hyperventilation syndrome include one or more of the symptoms of breathlessness out of proportion to physical effort, chest pain usually not typical of angina pectoris, dizziness, paresthesias, weakness and fatigue, and palpitations.[1-5] Hypocapnia induced by overbreathing initiates a sequence of physiologic changes responsible for most of the signs and symptoms; these changes may even produce bronchoconstriction[6] that may actually result in audible wheezing, contributing to the sensation of dyspnea as well as simulating or

intensifying preexisting asthma.[7] Anxiety, which accompanies this syndrome, usually induces a hyperadrenergic state,[8] producing symptoms that blend with the various clinical manifestations, and these may further confound the underlying pathogenesis. Often sighing excessively during interviews, the patient himself may fail subjectively to recognize the respiratory problem, having become preoccupied with the associated somatic symptoms. Because of rapid breathing through the mouth, the sensation of dryness of the mouth is a regular feature. The chest pain is often variable in nature, lasting from minutes to hours, often sharp and migratory, but it may occasionally closely resemble angina pectoris. The sensation of dizziness, or giddiness, sometimes resembles true vertigo, suggesting diseases that cause syncope or vestibular dysfunction. Symptoms may also be aggravated by upright posture, suggesting orthostatic hypotension.

Although the somatic sensations of numbness and tingling (paresthesias) are expected to be perioral in location, more often they affect the arms, hands, legs, and feet, occasionally dominant or exclusively localized to one side of the body—usually the left.[5,9] Additional symptoms include hot sensations, sometimes with diaphoresis, and feelings of chilliness. These sensations likely result from adrenergic stimulation combined with peripheral vasomotor changes.[10] Musculoskeletal pains, similar to those noted in the chest, may also occur in a variety of locations, such as the head and back. Nausea and symptoms consistent with aerophagia and globus hystericus are also commonly associated with the anxiety and rapid breathing.

Hyperventilation produces sinus tachycardia and other electrocardiographic changes,[11-15] most commonly downward shifts of ST segments with flattening of the T waves in the left precordial leads together with an apparent prolongation of the QT interval, changes resembling those of hypokalemia. Isolated T-wave inversions and marked ST depressions are less common. The ST shifts can closely simulate cardiac ischemic changes, but they are usually not induced—or are even *lessened*—by exercise.[11]

Previous studies indicate that hyperventilation syndrome is quite common: it has been observed in 6 to 10 percent of patients presenting to general internists,[1,2] with comparable numbers seen by consulting cardiologists and gastroenterologists.[15,16] This common occurrence accords well with the author's personal experience in a practice involved primarily in consulting cardiology.

Is "Neurocirculatory Asthenia" Nothing More than Hyperventilation Syndrome?

In a recent review, Paul[17] describes neurocirculatory asthenia as "a disorder of unknown origin, often familial, characterized by the presence of one or more symptoms including breathlessness with and without effort, palpitation, nervousness, chest discomfort not typical of angina pectoris, fatigability, and faintness." Although all these manifestations are typical of hyperventilation, virtually all authors fail to acknowledge this similarity, emphasizing instead the chronicity of symptoms and lack of specific treatment. Neurocirculatory asthenia, therefore, is probably nothing more than a form of hyperventilation syndrome. Obviously, there is need for a systematic study to test this hypothesis, but in the meantime, the individual clinician should carefully exclude the diagnosis of hyperventilation before applying the label of neurocirculatory asthenia.

Is the "Panic Disorder" Related to the Hyperventilation Syndrome?

Much attention has recently been devoted to a common condition called "the panic disorder." Beitman et al,[18] in a study of nonanginal chest pain, describe the panic disorder as attacks of "discrete periods of intense fear or discomfort, accompanied by at least four of the following symptoms: shortness of breath (dyspnea) or smothering sensations; choking; palpitations or accelerated heart rate (tachycardia); chest pain or discomfort; sweating; faintness; dizziness, lightheadedness, or unsteady feelings; nausea or abdominal distress; depersonalization or derealization; numbness or tingling sensations (paresthesias); flushes (hot flashes) or chills; trembling or shaking. . . ." These latter authors do not consider the possibility that hyperventilation could have caused many—if not all—of the multiple somatic symptoms! On the other hand, others[19,20] have suggested that panic attacks are inextricably associated with hyperventilation, in which the overbreathing induces disagreeable somatic symptoms that cause further anxiety, resulting in a vicious cycle of more frequent and severe attacks. I believe that this latter likelihood creates the need for each clinician to consider hyperventilation as an important contributor to the symptom complex of the panic disorder.

The Mitral Valve Prolapse Syndrome and its Relationship to the Hyperventilation Syndrome

Several studies[21] have suggested that mitral valve prolapse, a common congenital disorder, might be associated with—and possibly be the cause of—a variety of symptoms, including atypical chest pain, palpitation, dyspnea, anxiety and panic attacks, and electrocardiographic repolarization changes. Autonomic dysfunction, characterized by a hyperadrenergic state, has even been thought to occur in a high percentage of those studied, further supporting the contention that mitral prolapse is part of an underlying multisystem organic disorder or "syndrome."

Wooley[22,23] has even suggested that mitral prolapse accounts for all the manifestations previously attributed to neurocirculatory asthenia, panic disorder, and autonomic dysfunction states, thus advancing the hypothesis that the mitral prolapse syndrome had superseded all these other diagnostic categories. Controlled studies, however, have not supported a relationship between mitral prolapse and most of these "associated" signs and symptoms.[21] To this date, prolapse has been found to bear a direct statistical relationship to only systolic clicks, murmurs, thoracic bony abnormalities, palpitations (with tachyarrythmias), and a tendency toward lower systolic blood pressures.[21,24] Inasmuch as mitral prolapse is a common disorder, however, estimated to affect as many as 5 to 10 percent of the general population,[25] one would anticipate its frequent and fortuitous coincidence with symptoms of hyperventilation, another common disorder. The frequent occurrence of this combination would tend to support any preconceived misapprehension by the individual clinician who believes that mitral prolapse accounts for the variety of findings associated with hyperventilation—especially anxiety and chest pain.

The Relationship between Hyperventilation Syndrome and Noncoronary Chest Pain

Inasmuch as the hyperventilation syndrome is but one of many causes of chest pain, its importance as a causative factor in mixed populations of patients suffering from thoracic discomfort may vary greatly with patient selection. Nevertheless, available studies indicate that as many as 50 percent or more of individuals having noncoronary chest pain may have hyperventilation,[26,27] anxiety, and panic disorder.[18,28] Although the long-term survival of patients with chest pain and normal coronary arteries is excellent,[29-31] these individuals generally remain symptomatic if they are merely given reassurance that the coronary cineangiograms are normal.[28,31] The possibility that hyperventilation may be a leading cause of "occult" chest pain creates an opportunity to more effectively treat a sizeable portion of this group.

Recognition and Management of Hyperventilation

All patients considered to have any of the conditions described above (neurocirculatory asthenia, panic disorder, noncoronary chest pain, and mitral valve prolapse "syndrome") should be vigorously screened for hyperventilation. Obviously, the diagnosis rests on the reproduction of the same symptoms in the clinic when the subject is instructed to voluntarily hyperventilate. Simple explanation of the mechanism and respiratory control of these symptoms will usually provide complete relief. Even the underlying anxiety, as seen with panic attacks, may be ameliorated by management of the breathing disorder,[32-34] for the wide range of disagreeable symptoms brought on by overbreathing may actually contribute to the apprehension and panic. Although the chronic chest pain may be quite difficult to reproduce in the clinic and difficult to control, Evans and Lum[26] found that management aimed at restoring a normal breathing pattern was highly effective in eliminating this pain. Adjunctive pharmacologic treatment may be useful in difficult cases. β-Blockers tend to ameliorate the peripheral symptoms of anxiety,[35] such as palpitation and diaphoresis, and they may even reduce the respiratory stimulatory effect of catecholamines.[8] Tricyclic antidepressants are said to be especially useful in controlling the anxiety associated with panic attacks.[36]

Because of the confusion engendered by the nomenclature and descriptions of the various "organic" states described above, it is likely that a substantial proportion—probably even a majority—of individuals suffering from the hyperventilation syndrome are overlooked. I suspect that Lum[32] has concluded correctly that, because of its complex and pervasive nature, hyperventilation syndrome can fairly claim to have replaced syphilis as the great mimic of our time!

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