Specific heart disease in diabetes mellitus

Heart disease is a major cause of death in patients with diabetes mellitus, and the risk of atherosclerotic coronary artery disease is substantially increased in patients with both overt diabetes and asymptomatic hyperglycaemia. Recent epidemiological evidence from the Framingham study has confirmed the increased incidence of angina and myocardial infarction, especially in women, but has also suggested that the frequency of congestive heart failure is greater than that predicted from atherosclerotic risk factors. While most diabetics have more than average atherosclerosis, indistinguishable from that in non-diabetics, two separate theories have been advanced to explain the increased risk of cardiovascular disease: the presence of atherosclerosis or small vessel disease. Necropsy material from diabetics dying of unexplained congestive heart failure or myocardial infarction and angiographic studies of diabetics with chronic renal or heart failure have shown severe and widespread occlusive atherosclerosis of the coronary arteries. Other studies suggest, however, that heart failure may be attributed to small vessel disease of the coronary circulation—analogous to that found in the retina and kidney—with relatively normal coronary arteries at necropsy on angiography. Histological examination of the heart in diabetics shows abnormalities of the small vessels with intimal proliferation and thickened walls, perivascular and interstitial fibrosis, and accumulation of glycoproteins and lipids. Thickening of the capillary basement membrane, an ultrastructural hallmark of diabetes, has been found in a myocardium. A recent elegant study by Factor and co-workers showed capillary microaneurysms in necropsy specimens injected with silicone rubber, emphasizing that diabetic microangiography is widespread and that many tissues may be affected.

Non-invasive methods of assessing left ventricular function have confirmed that it is frequently impaired in young, asymptomatic diabetics, in maturity onset diabetics, and in those with retinopathy and nephropathy. A relation appears to exist between the extent of clinical microangiography and the degree of impairment of left ventricular function; diabetics with proliferative retinopathy and nephropathy have the most severe ventricular dysfunction. In diabetics the left ventricle is not dilated or hypertrophied, and abnormalities of function are predominantly in diastole, with delayed opening of the mitral valve and prolongation of the isovolumic relaxation time. Reduced ejection and abnormal systolic time intervals are probably late events. These diastolic abnormalities may be differentiated from those found in occlusive coronary artery disease, where incoordinate ventricular relaxation is the principal feature.

Furthermore, in addition to large and small vessel disease, diabetics have other reasons for their impaired left ventricular function: tissue perfusion and oxygenation are compromised by platelet and coagulation abnormalities, increased blood viscosity, and reduced erythrocyte deformability.

What are the prospects for prevention and treatment? Non-specific measures directed at reducing the risk of microangiopathy, such as close control of blood glucose, the vigorous treatment of hypertension (which may further impair left ventricular function directly), and discouragement of cigarette smoking are unproved but may help. Agents which modify the abnormal rheological features in diabetes are also being evaluated. Drugs and dietary manoeuvres that lower plasma lipid concentrations would be unlikely to influence the microvascular component of the disease, and in the absence of angiography due to coronary artery disease coronary artery bypass grafting has no value in impaired left ventricular function. No specific treatment exists, indeed, for severe left ventricular disease. Isolated reports that continuous subcutaneous infusion of insulin may reverse or prevent the progression of retinopathy suggest that the technique may have a similar protective effect on the small coronary arteries. Whether specific heart disease due to diabetic microangiopathy occurs in addition to or independently of coronary artery atherosclerosis remains uncertain, but left ventricular function is frequently found to be impaired in the absence of angiography or myocardial infarction. Simple non-invasive techniques for detecting abnormal left ventricular function may help differentiate these diabetics who are at low risk—and may look forward to a long period free from vascular complications—from those at high risk while clinically free from vascular disease.

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Motor neuron(e) disease

Even allowing for loss of the “e” in translation across the ocean, the apparently simple concept of Motor Neurone Disease is far from universally accepted within the constellation of motor neuron diseases.

We may without trepidation let “motor neurone diseases” refer to all disorders characterised primarily by progressive weakness attributed to lesions of the anterior horn cell, whether or not any other parts of the neuraxis are affected. The major groupings included in this definition are the heredofamilial spinal muscular atrophies, with their own subtypes both eponymous and numerical, and motor neuron disease; lead or mercury intoxication contributes small numbers.

Here I shall use motor neurone disease as a generic entity. Its components are, firstly, amyotrophic lateral sclerosis for the combination of lesions of the anterior horn cells and pyramidal tract; secondly, progressive myelopathic (spinal) muscular atrophy when lesions are limited to the anterior horn below the foramen magnum; and, thirdly, progressive bulbar palsy for anterior horn affections of the brain stem. A patient with both progressive bulbar palsy and progressive myelopathic muscular atrophy would arbitrarily be classified as progressive bulbar palsy. And it is in this context that most European workers have, at least until recently, used motor neurone disease. Nevertheless, in the colonies in particular there are still some rebels who prefer amyotrophic lateral sclerosis as the generic term regardless of the 1976 of Babinski. But further to confound the question there is one European centre which seems to employ motor neurone disease as precisely equivalent to Charcot’s disease of upper and lower motor neuron.

Appeal to the International Statistical Classification of Diseases, Injuries, and Causes of Death helps not at all. The new (9th) revision, in use since 1979, puts motor neurone disease and all its subtypes into one fourth-digit code under a three-digit rubric for “Anterior horn cell disease.” Earlier editions were more discriminating and more variable. Nevertheless, even accepting motor neurone disease—amyotrophic lateral sclerosis—progressive bulbar palsy—progressive myelopathic muscular atrophy does not solve our problems. There is “lytico,” nė “Guamanian amyotrophic lateral sclerosis,” or “the Marians Islands form of amyotrophic lateral sclerosis,” or “the Western Pacific form of amyotrophic lateral sclerosis.”

First described for Chamorro natives of the island of Guam, the entity clinically and—initially—pathologically appeared identical with sporadic motor neurone disease. It is known to affect natives of Rota and Saipan (thus “Marianas”), and there are also focsi of the identical disease within the Kii peninsula of south-eastern Honshu, Japan—plus another focus, without pathological proof, in certain villages of West New Guinea (thus “Western Pacific”). In these areas its occurrence is 20 to 50 times as common as is sporadic motor neurone disease. But more than frequency distinguishes this disorder. In the same places, and even in the same patients, there is another highly prevalent illness called the Parkinson-dementia complex, with a unique pathological character later discovered to be present even in those with the amyotrophic lateral sclerosis syndrome.1-3 Most recently there may be emerging a “Madras amyotrophic lateral sclerosis,” a sporadic disorder which adds sensorineural deafness to the clinical constellation of slowly progressive motor neurone disease. And large clinic series in the Occident may include perhaps 10% or fewer in whom motor neurone disease is inherited as an autosomal dominant trait.

Nevertheless, the great bulk of the patients we see with motor neurone disease are of unknown origin and implacable progression, unaltered by treatment. Epidemiologically, this “true” motor neurone disease seems to be distributed uniformly about the world. Death rates within and among countries are for the most part between one and 1-5 per 100 000 population a year. Almost all deaths are now attributed to amyotrophic lateral sclerosis. There is consistent male excess at 1:5 to 1. In the United States there is also white:non-white differences of about 1:6:1. The age-specific rates rise from almost nil near age 50 to a sharp maximum at age 70. This configuration holds for all lands and both sexes and colours.

Average annual incidence rates for motor neurone disease or amyotrophic lateral sclerosis are also mostly about one to 1-5 per 100 000 population; point prevalence rates range from one to seven per 100 000, but the more complete studies suggest a prevalence of some five per 100 000. Age specific incidence