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Cardiovascular involvement in primary systemic vasculitis

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The primary systemic vasculitides are a group of autoimmune conditions characterised by occlusion, stenosis or aneurysmal dilatation of blood vessels secondary to intra-mural inflammation. Current therapy has converted the outlook of these diseases from death or severe morbidity to a remitting–relapsing condition in most instances. Longer survival, relapsing course of disease and chronic glucocorticoid therapy probably contribute to an increase in cardiovascular events and morbidity. This article reviews the available data for effect of primary systemic vasculitis on cardiovascular end points like coronary artery disease, congestive cardiac failure, hypertension and aortic aneurysm in all age groups. We examine the interplay between the activated endothelium, autoimmune mechanisms and treatment factors to produce a direct insult or increased atherogenic potential of primary systemic vasculitis. Recommendations to deal with cardiovascular end points are made.

The primary systemic vasculitides (PSVs) are a group of autoimmune conditions characterised by occlusion, stenosis or aneurysmal dilatation of blood vessels secondary to intra-mural inflammation. There have been several proposals to classify and name distinct vasculitic syndromes for the purpose of clinical studies [1–4]. Although each classification system has its limitations, it is agreed broadly that the PSVs can

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be divided into small-, medium- and large-vessel vasculitides [2,5,6]. Amongst them, Wegener's Granulomatosis (WG), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS) have a strong association with the presence of anti-neutrophil cytoplasm antibodies (ANCAs) [7]. Together, the three syndromes are termed the ANCA-associated vasculitides (AAV). However, these three syndromes behave differently and have different long-term outcomes [8]. The annual incidence of PSVs in northern Europe is 40–54 patients/million [9]. The exact incidence of each form of vasculitis can vary depending on age, sex, ethnicity, geography, time of the year and other environmental factors [10]. The classification system used also has a bearing on the incidence of a specific vasculitic syndrome [11].

PSVs can be life-threatening or organ-threatening. Current therapy has converted the outlook of these diseases from death or severe morbidity to a remitting–relapsing condition in most instances. Longer survival, relapsing course of disease and chronic glucocorticoid therapy probably contribute to an increase in cardiovascular events and morbidity.

There are very few data relating to cardiovascular sequelae associated with vasculitis in the young. Most studies relate to Kawasaki disease (KD), or Henoch–Schönlein purpura (HSP) although limited data are emerging in relation to other childhood vasculitic syndromes. This article reviews the role of disease and treatment factors in increasing the burden of cardiovascular disease in PSVs, and possible strategies to manage or modify the cardiovascular risk. For the purposes of this article, we will concentrate on coronary artery disease, congestive cardiac failure, hypertension and aortic aneurysm in all age groups.

Aetiopathology of cardiovascular involvement in PSVs

The endothelium

Endothelial involvement has long been recognised in vasculitis [12] but the precise mechanism of activation and damage differs in the different syndromes of the disease. There are a variety of mechanisms by which endothelial activation and damage may occur. Complement-dependent cytotoxicity, antibody-dependent cytotoxicity, direct effect of adhesion molecules and cytokines have all been implicated. Immune complex-mediated activation of complement has been implicated in polyarteritis nodosa (PAN) [13]. ANCAs are actively involved in the neutrophil–endothelial interaction which results in endothelial activation and damage [14]. Anti-endothelial cell antibodies, a family of different antibodies binding to a variety of endothelial antigens, have been detected in many forms of vasculitis [15] but their exact mechanism of action, if any, is unclear. The endothelium actively interacts with endothelial adhesion molecules, leucocytes and cytokines to produce an amplification of the inflammatory cascade [16].

The impact of chronic inflammatory disease and the atherogenic potential of primary systemic vasculitis

Chronic rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus, are associated with increased cardiovascular disease and mortality [17,18]. It has been suggested that this may be due to secondary vasculitis and endothelial dysfunction [19]. Survival from PSV has greatly improved as a result of immunosuppressive therapy, converting it into a chronic disease with episodes of relapse [20]. The disease is associated with high circulating levels of C-reactive protein (CRP), which has been shown to be independently associated with cardiovascular disease in patients with PSVs and healthy individuals as well [21].

Patients with Takayasu's arteritis (TAK) have been shown to have accelerated atherosclerosis in their carotid arteries, comparable to patients with systemic lupus erythematosus, and significantly greater than healthy controls [22]. Calcific deposits are reported on computed tomography of the aorta in TAK [23]. The role of PSVs causing accelerated atherosclerosis is demonstrated in long-term studies of patients with KD. Dhillon studied vascular responses to reactive hyperaemia in the brachial artery using high-resolution ultrasound [24]. Flow-mediated dilation (FMD, an endothelial-dependent response) was markedly reduced in KD patients compared with control subjects many years after the illness, even in patients without detectable early coronary artery involvement. In contrast, Ikemoto demonstrated impaired FMD only in patients with persistent coronary artery lesions (CAL) [25]. Additionally, another recent cross-sectional study by McCrindle failed to demonstrate differences in brachial artery reactivity (BAR) following KD, as compared to controls [26]. Issues relating to inherent