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Inflammation in ischaemic heart disease

C Reactive protein concentrations may provide useful information on risk

See p 1061

Recent reports have suggested a link between blood concentrations of C reactive protein and the risk of cardiovascular disease. The ECAT study (European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study) followed 3000 people with chronic stable ischaemic heart disease for three years and found a significant correlation between concentrations of C reactive protein within the normal range and long term cardiovascular risk.[1] Raised concentrations have also been shown to be strong prognostic indicators in patients with unstable angina, [2] and in this week's *BMJ* Mendall *et al* report an association between C reactive protein concentrations and indirect evidence of ischaemic heart disease (p1061).[3] What are the pathogenetic implications of this novel marker of acute and chronic manifestations of ischaemic heart disease and its relevance in clinical practice?

Mendall *et al* studied 303 men aged 50-69 years selected from general practice registers[3] and found that the prevalence of indirect evidence of ischaemic heart disease and a history of claudication (together with age, smoking, chronic bronchitis, and most traditional cardiovascular risk factors) increased progressively as blood concentrations of C reactive protein rose. This correlation between C reactive protein and traditional risk factors for ischaemic heart disease may influence prognosis in the long term by favouring the development of atherosclerosis, but the prognostic value of C reactive protein might also result from an increased incidence and worse outcome of acute phases of instability, which are now known to be unrelated to the severity or to the worsening of organic stenoses.

The findings of Mendall *et al* and the long term prognostic value of mildly raised concentrations of C reactive protein observed in the ECAT study[1] are in line with the striking short term prognostic value of very high concentrations of C reactive protein and serum amyloid A protein in patients with unstable angina.[2] Two recent studies from our group suggest how they might be related: both showed that mildly raised concentrations of C reactive protein may indicate enhanced production of interleukin 6 in response to different stimuli.

In the first study C reactive protein and interleukin 6 (a cytokine responsible for acute phase protein production by the liver) were assessed serially in 22 patients with chronic stable angina and in 32 patients with unstable angina before and 6, 24, 48, and 72 hours after successful single vessel coronary angioplasty. The study showed that coronary angioplasty caused a sharp increase in concentrations of interleukin 6 (a cytokine responsible for acute phase protein production by the liver), followed by a rise in concentrations of C reactive protein, but only in patients with raised baseline concentrations of C reactive protein.[4] In the second study venous blood samples were taken on admission, at 6, 24, 48, and 72 hours, and at discharge in 35 patients with acute myocardial infarction admitted to our coronary care unit within three hours of the onset of symptoms. The study showed that patients with raised concentrations of C reactive protein very early after the onset of symptoms (when troponin T was still negative) had a much higher peak value of C reactive protein than those with normal values on admission, in spite of similar infarct sizes as assessed by levels of creatine kinase.[5] Other stimuli that might be responsible for the enhanced production of interleukin 6 are cytomegalovirus, *Helicobacter pylori*, or *Chlamydia pneumoniae* infection as suggested by Mendall *et al*.[3] Thus multiple mechanisms may exist through which the acute phase response (in particular raised concentrations of C reactive protein) is related to short term prognosis, and an understanding of these mechanisms is essential for the development of specific treatments and preventive strategies.

So far the greatly increased concentration of C reactive protein in patients with unstable angina remains unexplained. It cannot be attributed to the severity of atherosclerosis, as there is no correlation in patients with chronic stable angina[2]; to minor degrees of myocardial necrosis, as troponin T concentrations are not raised[2]; to prolonged ischaemic episodes, as C reactive protein values remain low in patients with variant angina (characterised by severe transmural myocardial ischaemia associated with transient ST segment elevevation on the electrocardiogram and caused by occlusive epicardial coronary artery spasm)[6]; to episodic activation of the haemostatic system, as thrombin activation does not increase plasma concentrations of C reactive protein[7]; or to reactivation of dormant cytomegalovirus, as mRNA cytomegalovirus was not found in specimens of atherosclerotic plaques taken at directional coronary atherectomy from patients with unstable angina.[8] Indeed, most patients with unstable angina have raised concentrations of C reactive protein for months after symptoms develop, independent of the severity of their coronary atherosclerosis, and while concentrations remain raised the risk of new episodes of instability and of myocardial infarction is greatly increased.[9]

Interleukin 6 and its main trigger, tissue necrosis factor, have intense proinflammatory and procoagulant properties. Thus these cytokines may activate the endothelium to produce powerful vasoconstrictor substances, expose adhesive receptors for leucocytes, and become thrombogenic, thereby explaining the presence of coronary thrombi in the absence of plaque fissure or rupture. Nevertheless, an acute phase response cannot account for all acute coronary syndromes as

Liuzzo *et al* found that 24% of patients with myocardial infarction did not have raised C reactive protein values on admission.[2]

We are undertaking a prospective multicentre study of 2000 patients with unstable angina sponsored by the Italian National Research Council to assess the incremental prognostic value of markers of the acute phase response and their correlation with conventional risk factors and with the mechanisms that lead to enhanced production of C reactive protein. This study should improve our understanding of the role of inflammation. In the meantime what conclusions can we draw from available evidence about the usefulness of C reactive protein measurements?

Blood concentrations of C reactive protein (and possibly of serum amyloid A protein) may provide useful information beyond that available from the clinical presentation and other tests in two conditions. In patients presenting with unstable angina C reactive protein concentrations greater than 3 mg/l, and especially greater than 10 mg/l, predict a poor response to intensive medical treatment and indicate high risk of myocardial infarction. Such patients should be given intensive medical treatment but also be considered for urgent revascularisation. In patients with chronic ischaemic heart disease C reactive protein measurements identify a gradient of risk for myocardial infarction or cardiovascular death. The risk of these outcomes over three years rises from 0% in patients in the upper third of cholesterol concentrations (> 263 mg/dl) but the lower third of C reactive protein and fibrinogen concentrations to 10% in patients in the highest third of both cholesterol and C reactive protein and fibrinogen values. In this second, high risk, group reducing cholesterol concentrations may have a much greater effect in reducing the incidence of events than in the first group, who appear to be at a considerably lower risk.

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Managing peanut allergy

Demands aggressive intervention in prevention and treatment

See p 1074

The average American now ingests about 11 pounds (5 kg) of peanut products each year (United States Peanut Council, personal communication), about 55% as peanut butter and the rest in sweets, baked goods, and table nuts. As the American lifestyle has become more frenetic over the past 20 years, peanut products (such as peanut butter crackers, peanut butter and jelly sandwiches, and peanut butter sweets) have increasingly served as "snacks" or "quick meal substitutes" replacing more standard mealtime fare. Consequently, infants and young children are being exposed to peanut products earlier in life.

A study examining the efficacy of food allergen avoidance in preventing atopic disease in infants defined as being at high risk for atopy found that of 185 control infants, 80% had been exposed to peanut products by their first birthday and 100% by their second birthday.[1] Follow up at 7 years of age revealed that about 7% of high risk children had positive skin tests to peanut and 4% were felt to be reactive on the basis of history or oral food challenges.[2] The prevalence of peanut allergy seems to have increased over the past two decades. In comparable groups of children referred to us for evaluation of severe atopic dermatitis and possible food allergy, peanut sensitisation (positive skin prick test) increased by 55% while allergic reactions increased by 95% over a 10 year period. Today peanuts are believed to be one of the leading causes of food allergic reactions in the United States[3 4] and, together with tree nuts, are probably the leading cause of fatal and near fatal anaphylaxis induced by food.[5-8]

It has long been assumed that peanut allergy was largely an American problem, but press reports in 1993 of six deaths due to peanut allergy in Britain made it apparent that the problem was no longer confined to the North American continent. An article in this issue of the *BMJ* addresses the scope of the problem in Britain. Ewan (p 1074) reports 62 cases of peanut and/or nut allergy evaluated in a one year period. Peanuts accounted for nearly half of the allergies, with 55% of the allergies presenting by age 2 years and 92% by age 7 years. The author concludes that peanut allergy is occurring in very young children, that people allergic to peanuts are at increased risk of nut allergies, that peanut and nut allergy are rarely "outgrown," and that the prevalence of peanut and nut allergy is increasing.[9] This is certainly in agreement with our data and those of other investigators in the United States (SA Bock, AW Burks, R Zeiger, personal communication). With this rising number of individuals at risk for potentially lethal reactions, aggressive intervention in both prevention and treatment is essential.

Firstly, some measures should be instituted in an attempt to stem the increasing prevalence of peanut and nut allergy. Infants at increased risk for developing peanut or nut allergy should be identified. These are infants from atopic families or families with other food allergies or atopic disorders. Their parents should be advised to eliminate all peanut products from the child's diet for at least three years, and mothers who are breast feeding should eliminate peanut products from their own diet. Children under 3 years of age who are being evaluated for other allergies should be tested for peanut allergy, and any child with peanut specific IgE antibodies should avoid all peanut and nut products for three to five years. If no reactions to inadvertent ingestions have occurred in the interim, the