19-022

INCREASES OF PR3 AND MPO GENE TRANSCRIPTION IN CIRCULATING LEUKOCYTE OF ANCA-ASSOCIATED DISEASE CORRELATE WITH DISEASE ACTIVITY

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Proteinase (PR3) and myeloperoxidase (MPO) are the primary autoantigens of anti-neutrophil cytoplasmic autoantibodies (ANCA). PR3 has been reported to be present on the surface of polymorphonuclear neutrophils and monocytes, and to exist in the circulation of patients with active ANCA vasculitis and glomerulonephritis (ANCA-GN). We investigated circulating leukocytes from patients with ANCA-GN for changes in levels of PR3 and MPO mRNA transcripts.

Leukocytes were isolated from 46 blood samples of patients with ANCA-GN (PR3-ANCA n=29; MPO-ANCA n=17); 24 samples from healthy donors served as normal controls, and 25 samples from end-stage renal disease (ESRD) and 17 samples from systemic lupus erythematosus (SLE) patients as disease controls. The mRNA levels of PR3 and MPO were measured by TaqMan quantitative PCR. The data are expressed as relative fold-change, as compared to a healthy control reference sample.

The relative levels of PR3 mRNA increased significantly to 20.5 ± 28.7-fold ($P < 0.05$) in patients with active ANCA-GN, above that in healthy donors (0.6 ± 0.6-fold) (active+: 2.9 ± 2.3, $P < 0.05$; active++: 16.7 ± 27.3, $P < 0.05$; active+++: 37.3 ± 32.4, $P < 0.05$). PR3 mRNA did not increase in ANCA patients in remission (3.8 ± 4.7, $P > 0.05$), ESRD (1.6 ± 3.2, $P > 0.05$) or SLE patients (1.0 ± 1.4, $P > 0.05$). MPO mRNA levels markedly increased (13.9 ± 21.8, $P < 0.05$) compared to healthy donors (0.9 ± 0.8) (active+: 3.9 ± 4.6, $P > 0.05$; active++: 12.8 ± 22.1, $P < 0.05$; active+++: 33.9 ± 27.0, $P < 0.05$), but not in ANCA patients in remission (2.8 ± 2.5, $P > 0.05$), ESRD (2.1 ± 3.6, $P > 0.05$) or SLE (1.8 ± 2.4, $P > 0.05$). There was a positive correlation between the increase in PR3 mRNA and the increase in MPO mRNA ($R^2=0.82$, $P < 0.0001$), regardless of whether the patient was PR3- or MPO-ANCA-positive.

In conclusion, these data indicate that ANCA-GN is associated with an increase of PR3 and MPO mRNA expression by peripheral blood leukocytes. PR3 and MPO mRNA levels may be a marker for disease activity in ANCA-GN.

20-119

CARDIAC INVOLVEMENT IN WEGENER'S GRANULOMATOSIS: ECHOCARDIOGRAPHIC FEATURES AND CLINICAL OUTCOMES

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Background: The spectrum of extra-cardiac disease in Wegener's granulomatosis (WG) has been well described. However, cardiac involvement in WG has not been systematically studied and remains poorly understood.

Methods: Review of echocardiographic and clinical data of 85 consecutive patients with proven WG over 21 years. Cardiac abnormalities at echocardiography were analyzed at the time of the diagnosis of WG. Echocardiographic lesions were attributed to WG when no other coexisting disease could explain them, or when objective data such as resolution of the lesion with immunosuppressive therapy was documented. Follow-up data were obtained by reviewing the patients' last recorded visit or correspondence with Mayo Clinic.

Results: Echocardiographic abnormalities were found in 73 patients (85.8%). In 26 patients (31%), lesions appeared directly related to WG. Of these, regional wall motion abnormalities (RWMA) were the most frequent abnormalities found in 16 patients (61.5%); the ventricular septum was most consistently involved (50%), followed by the inferior (42%), apical (34%), anterior (30%), and lateral wall (26%). Left ventricular (LV) systolic dysfunction with a mean ejection fraction of 46% ± 14% was found in 13 (50%) and pericardial effusion in 5 (19%) patients. Other findings included acute aortic regurgitation, LV aneurysm, intracavitary thrombus, and a large mass in the LV outflow tract. There was a 42% increased mortality in patients with WG cardiac involvement at echocardiography compared to patients with abnormal echocardiograms from other causes (RR 2.9). Cox regression analyses showed that cardiac WG was a univariate predictor of poor survival.

Conclusion: We found a high frequency of echocardiographic abnormalities in WG. These lesions seem to be directly related to WG and associated with increased mortality. Because cardiac involvement of WG can be clinically silent, associated with significant morbidity and portend worse prognosis, echocardiography screening in active WG may be of clinical value.

21-041

ENDOTHELIAL MICROPARTICLES: JUST BLOOD "DUST," OR A "MUST" FOR THE DIAGNOSIS AND MONITORING OF DISEASE ACTIVITY IN CHILDHOOD VASCULITIDES?

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Introduction: Microparticles (MPs) are released from endothelial cells in response to a variety of injurious stimuli and recently have been shown to be increased in multiple sclerosis and antiphospholipid syndrome.

Aims: This study examined endothelial and platelet MP profiles in children with systemic vasculitis (SV) to test the hypothesis that endothelial MPs may provide a tool for the diagnosis and monitoring of disease activity.

Patients: 12 children with active SV (9 with polyarteritis, 2 with Kawasaki disease, and 1 with hypersensitivity vasculitis); 8 children with inactive SV; 8 disease control children without SV; and a control group of 28 healthy subjects comprising 11 healthy children and 17 young adults were studied. Additionally, paired samples from 4 children with SV pre and post induction of remission were examined.

Methods: Plasma was centrifuged at 13,000G for 60 min-

utes, and the pellet resuspended and prepared for flow cytometry. MPs were defined as particles less than 2 microns in diameter and with surface binding of annexin-V. Fluorescent conjugated monoclonal antibodies to several endothelial markers and platelet markers were used to identify and quantify MPs.

Results: Plasma from patients with active vasculitis contained a 12.4-fold elevation of E-selectin positive endothelial MPs compared with patients in remission (p=0.001), a 5.7-fold elevation compared with controls (p=0.000) and a 7.9-fold elevation compared with disease controls (p=0.001). A similar result was obtained for MPs expressing the endothelial marker CD105. No difference was observed for MPs of platelet origin between the groups. 4/4 patients with active vasculitis demonstrated high levels of endothelial MPs which fell to normal following induction of remission (a 10.5-fold decrease for CD105 MPs and an 8.7-fold decrease for E-selectin MPs).

Conclusion: Endothelial MPs may provide a "window" to the activated endothelium, and these preliminary data suggest that they may be useful diagnostically and for the monitoring of disease activity in SV of childhood.

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