Title: Inflammation and Arterial Stiffness in Patients with Chronic Fatigue Syndrome

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Background: Chronic fatigue syndrome (CFS) is characterized by lipid peroxidation with elevated levels of F2-isoprostanes that correlate with post-exertional myalgia and we postulated that CFS was pro-inflammatory with many patients in a pro-oxidant state consistent with significant cardiovascular risk [1]. C-reactive protein (CRP) is an acute phase protein and a sensitive, non specific biochemical marker of chronic inflammation with highly sensitive assays shown to be a robust and independent predictor of cardiovascular risk. Markers of inflammation, including raised CRP levels, have already been demonstrated in some CFS patients [2] but little is known about the relationship between chronic inflammation and prognostic indicators of cardiovascular risk in CFS. Van de Putte, et al [3] reported increased arterial stiffness in a cohort of 32 adolescent CFS patients, aged 12 to 18 years, that was not associated with changes in arterial wall characteristics or lifestyle changes. Given the association between inflammation and increased arterial stiffness in other patient populations, and the recent evidence that increased arterial stiffness is an independent predictor of adverse cardiovascular outcome, we sought to investigate the relationship between CRP levels and arterial stiffness in well characterized CFS patients.

Methods: Forty one CFS subjects (age: 19-63 years) satisfied 1994 CDC criteria for CFS after a medical examination by one physician (CU) and 35 healthy volunteers served as controls. The local medical ethics committee approved the study and all volunteers gave informed consent. CRP (high sensitivity ELISA), 8-iso-prostaglandin $F_{2\alpha}$ isoprostanes, total and high density lipoprotein (HDL) cholesterol, and oxidised low density lipoprotein (oxLDL) were assayed from plasma stored at -70°C. Arterial stiffness was measured by the SphygmoCor pulse waveform analysis system. Peripheral pressure waveforms were recorded at the radial artery by applanantion tonometry using a high fidelity micromanometer. At least 15 high quality pressure waveform recordings were obtained from which the central aortic pressure waveform was calculated using a validated generalised transfer function.

Results: CFS patients had significantly increased levels of CRP ($P<0.01$) and 8-iso-prostaglandin $F_{2\alpha}$ ($P<0.005$). Pulse wave analysis revealed significantly greater augmented pressure (AP) and augmentation index (AIx) in CFS patients than in control subjects ($P=0.045$ and $P=0.036$, respectively) with AIx 39% higher in the CFS patients. Since AIx is influenced by heart rate, which was significantly higher in CFS patients, an index normalised for 75 beats per minute was used to provide a better comparison of arterial stiffness between CFS patients and control subjects. This index, AIx@75, was also significantly greater in CFS patients than in control subjects, but the difference (61%) was greater than for the unadjusted AIx (39%). AIx@75 showed the strongest correlations with systolic blood pressure, CRP, isoprostanes and oxLDL, however, in a multiple regression model the significant correlation between AIx@75 and systolic blood pressure, isoprostanes and ox LDL was removed and the only remaining significant determinant of AIx@75 was CRP ($\beta=0.449$, $P=0.007$).

Conclusion: CFS patients have significantly increased levels of plasma hs-CRP, $F_{2\alpha}$ isoprostanes and oxLDL that correlate positively with arterial stiffness. In a multiple regression model CRP is the strongest predictor of arterial stiffness conferring a significantly increased risk of a future cardiovascular event for CFS patients.

References:

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