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LETTER TO THE EDITOR

Cardiac sympathetic innervation associates with autonomic dysfunction in chronic fatigue syndrome – a pilot study

Despite hemodynamic abnormalities being well documented in chronic fatigue syndrome (CFS), it remains unclear the nature of the underlying autonomic nervous system problems that underpin these findings. Studies performed in subgroups of those with CFS suggest cardiac sympathetic denervation.

Meta-iodo-benzylguanidine (MIBG) imaging provides a quantitative measure of cardiac sympathetic innervation. Clinically, cardiac MIBG scanning is used to estimate local myocardial sympathetic nerve damage in heart disease and dysautonomia, particularly abnormalities arising due to sympathetic innervation [1,2]. In this study, we explored potential mechanisms that underpin the autonomic abnormalities seen in CFS using I125 MIBG participants that fulfilled Fukuda diagnostic criteria for CFS [3]. Participants were excluded if screened positive for a major depressive episode (Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders). Fatigue was measured using the Fatigue Impact Scale (FIS).

Autonomic function was measured continuously during 10 minute supine rest using the Taskforce Monitor (CNSystems; Graz, Austria) to derive heart rate and blood pressure variability and baroreflex sensitivity (BRS) (spectral analysis and the autoregressive model). Low frequency (LF) and high frequency (HF) bands were reported for heart rate, systolic and diastolic blood pressure variability and LF/HF ratio. These variability indices reflect autonomic control, with greater HF values reflecting greater vagal (parasympathetic) modulation and higher LF values indicating predominantly sympathetic modulation. The LF/HF ratio has been argued to capture 'sympathovagal balance' and higher values suggest greater sympathetic dominance [4].

Myocardial innervation imaging with Iodine-123-meta-iodo-benzylguanidine (123 I-MIBG) scintigraphy provides a non-invasive tool for the investigation of cardiac sympathetic innervation. MIBG is an analogue of guanethidine and is taken up by the post-ganglionic presynaptic nerve endings of the adrenergic nervous system. After depolarisation, MIBG is released into the synaptic cleft like noradrenaline but is not metabolised. Labelling MIBG with iodine-123 (123-I) permits visualisation of adrenergic innervation *in vivo* [5]. During the scintigraphic method of myocardial imaging 123-I-MIBG is intravenously administered at rest and imaging is performed after 10–30 minutes. Planar images with anterior views are used to evaluate cardiac sympathetic function. Regions of interest are set in the heart and mediastinum to obtain mean counts in each, after which H/M ratios are calculated to provide a degree of accumulation in the heart. Upper limit of normal is defined as <2.6. Increased sympathetic activity is associated with a low myocardial MIBG. Statistical analysis was performed using GraphPad PRISM.

Nine CFS subjects underwent MIBG. Mean ± SD age 51 ± 6.7 with five females. Length of history was 17 ± 11 years (range 7–28). Mean H/M ratio was 2.94 ± 0.7 with 6/9 (67%) of the CFS patients having values above the upper limit of normal.

There were no significant correlations between MIBG findings and length of history (data not shown). There were significant correlations between H/M ratio and BRS at rest ($p = .008$;

$r = 0.8$) and between increasing parasympathetic function measured as HF heart rate variability ($p = .03$; $r = 0.7$).Increasing H/M ratio associated with an associated shift in sympathetico-vagal balance ($p < .04$ $r = -0.7$) measured using the LF/HF ratio for heart rate variability and diastolic blood pressure variability. Increased cardiac sympathetic innervation measured using MIBG were also associated with lower fatigue severity ($p = .04$; $r^2 = 0.5$).

Impaired cardiac 123-I-MIBG uptake was associated with increased fatigue severity in CFS. This study suggests that the autonomic dysfunction seen in CFS patients might, in part, be related to abnormalities in cardiac sympathetic innervation which has symptomatic consequences for those affected.

By excluding CFS patients with comorbid depression we can be confident our findings are unrelated to current depressive illness. Also the lack of relationship with length of disease suggests that de-conditioning is an unlikely cause. We believe the associations between cardiac sympathetic innervation and the peripheral autonomic abnormalities seen frequently in CFS could be the cause of these abnormalities and represent a potential therapeutic opportunity.

An increase in MIBG uptake may be due to increased neuronal activity leading to increased active transporter uptake or higher density of sympathetic neurons. Chronic, unregulated, increase in sympathetic outflow may result in desensitisation of post-synaptic adrenergic receptors manifesting as attenuated sympathetic responses. Previous studies have confirmed that cardiac sympathetic denervation associates with fatigue [6] At this stage we cannot address causation as this study is small. It is suggested that our findings merit replication in other well characterised cohorts.

Our findings of a relationship between cardiac sympathetic innervation and autonomic dysfunction are consistent with previous studies [7] and suggest that CFS subjects demonstrate disturbed myocardial adrenergic innervation and adrenergic innervation defects.

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