Remedying Pain

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Chronic Fatigue: It's Mental!

Practitioners beware: chronic fatigue in developing countries, frequently assumed to be the result of nutritional deficiency or anemia, may instead be due to mental health issues. Vikram Patel et al[1] recently published a study in which they linked chronic fatigue with psychological and social factors.

The study consisted of about two-and-a-half thousand female participants, aged 18-50 years, from Goa, India. Data was collected through interviews of personal and health histories, measurements of hemoglobin concentrations from blood samples, and general medical examinations. Among the participants, 12% (11% to 13%) reported chronic fatigue, defined by the investigators to be an experience of fatigue (feeling tired and/or lacking in energy) for a minimum duration of the previous six months.

The investigators did find that participants who were older, who had experienced hunger in the previous three months, and those facing socioeconomic difficulties were significantly more likely to experience chronic fatigue. After adjusting for such variables, however, they discovered even more significant associations with gender disadvantages and mental health factors. For example, those women who lived in unhappy marriages, were sexually or verbally abused, or had concerns about their husband's extramarital affairs or habits were more prone to report prolonged fatigue. Most importantly, symptoms related to common mental disorders, such as depression and anxiety, and somatoform disorders were determined to be the greatest risk factors for chronic fatigue (two tailed p values < 0.001). On the other hand, no association was found between hemoglobin concentrations and chronic fatigue.

1. Patel V, Kirkwood BR, Weiss H, Pednekar S, Fernandes J, Pereira B, et al. Chronic fatigue in developing countries: population based survey of women in India. BMJ 2005; 330:1190-.

Got an AA Aneurysm?

With 1-3% of men over 65 years of age affected by ruptured abdominal aortic aneurysms, and death occurring in 70-95% of such cases, the question of screening is clearly raised. Jes Lindholt et al[1] conducted a randomized controlled trial to determine the effectiveness of just such a policy.

In the study, they screened a total of about five thousand Danish men aged 64-73 for abdominal aortic aneurysms using ultra-sonography. They detected an abdominal aortic aneurysm in 191 (4.0%) of the participants. An aneurysm was considered to be present if the infrarenal aortic diameter was $\geq$3 cm; those with aneurysms $\geq$5 cm were referred to a vascular surgeon, while the rest were offered annual scans. Participants, randomized to either the screening or no-screening groups, were followed up for a mean period of 52 months. Compared to the control group of over six thousand men, the screened group underwent significantly fewer (75% less, p=0.002) emergency operations, and had reduced specific mortality due to such aneurysms (67% less, p=0.003). Furthermore, throughout the follow-up time, only 9 deaths due to abdominal aortic aneurysm occurred in the screened group, compared to 27 in the control group. They calculated that the number needed to screen to save one life was 352. The investigators also determined from the study that rescreening patients with an aortic diameter of less than 25 mm seemed unnecessary, but those with diameters between 25 and 29 mm should be rescreened after 5 years.

Thus, this study demonstrates that routine screening for abdominal aortic aneurysm in men aged 64-73 years is worth considering.

1. Lindholt JS, Juul S, Fasting H, Henneberg EW. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. BMJ 2005;750.

Ouch, My Knee Hurts!

Increasing numbers of patients are experimenting with acupuncture in the hopes of alleviating chronic pain problems. Witt et al[1] conducted a randomized controlled trial to determine the effectiveness of this treatment for osteoarthritis of the knee.

A total of about 300 patients, aged 50-75 years and who had been diagnosed with osteoarthritis according to the American College of Rheumatology criteria, were randomly assigned to one of three groups: acupuncture, minimal acupuncture (superficial needling at non-acupuncture points), or a waiting list control.

Patients in the acupuncture and minimal acupuncture groups received treatment in 12 sessions of 30-minute duration over an 8-week period. All patients completed standard questionnaires at baseline, after 8 weeks, 26 weeks, and 52 weeks to assess degree of pain experienced.

Using the WOMAC (Western Ontario and McMasters Universities) Osteoarthritis Index as the primary outcome measure, investigators found that patients with osteoarthritis of the knee who received acupuncture had significantly less pain after 8 weeks than did patients who received minimal or no acupuncture (mean WOMAC indices of 26.9 in the acupuncture group, 35.8 in the minimal acupuncture group, and 49.6 in the waiting list control). Thus, the difference between the acupuncture vs minimal acupuncture was -8.8 ($p<0.0001$). The percentage of patients using analgesics in the acupuncture and minimal acupuncture groups decreased between weeks 1 and 8 (from 42% to 22% and from 38% to 23% respectively). However, after 52 weeks the difference between the acupuncture and minimal acupuncture groups was no longer significant ($p=0.08$).

1. Witt C, Brinkhaus B, Jena S, Linde K, Streng A, Wagenpfeil S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. Lancet 2005;366:136-43.

Can't Breathe? Try GSNO

Ever have trouble breathing? You may be missing an endogenous bronchodilator, S-nitrosoglutathione (GSNO), in your airways.

While most studies on allergic asthma have centered on the roles of bronchoconstrictors and inflammatory mediators on airway hyperresponsivity, Que et al[1] took a different approach and chose instead to investigate the effects of endogenous bronchodilators, specifically GSNO, in the disorder. To do so, they compared the effects of allergen challenge between the airways of wild-type mice and mice in which they deleted the gene for GSNO reductase (GSNOR), the enzyme that controls levels of GSNO in the body. Through a series of experiments, they discovered that, after allergen challenge, wild-type mice with airway hyperresponsivity (AHR) demonstrated increased levels of airway GSNOR and are depleted of lung S-nitrosothiols (SNOs). In contrast, the GSNOR$^{-/-}$ mice were found to have higher levels of lung SNOs after allergen challenge and actually appeared to be protected from AHR. Interestingly, the airway GSNO in these GSNOR$^{-/-}$ mice appeared to originate from nitric oxide (NO), of which elevated levels are generally a signature of asthma, derived from cytokine-inducible NO synthase (iNOS).

Additionally, investigators found that the protection from asthma in GSNOR$^{-/-}$ mice does not reflect a suppressed immune response to allergen; instead, it appears that SNOs are able to maintain airway patency even when inflammation occurs. All in all, Que et al's reports open up new avenues in our search of therapeutic approaches to alleviating airway obstruction in asthma.

1. Que LG, Liu L, Yan Y, Whitehead GS, Gavett SH, Schwartz DA, et al. Protection from Experimental Asthma by an Endogenous Bronchodilator. Science 2005;308:1618-21.

Something Smells Fishy Around Here

The inflammatory process is critical and must be robust in order to repair damage and protect humans from infections; however, dysregulated inflammation is the underlying factor of many human diseases. Numerous studies, including Serhan et al's recent experiments, suggest that omega-3 fatty acids found in fish oil have a variety of favorable health effects. Serhan et al[1,2] describe an 'off' switch for inflammation that has been derived from the same pathways that generate pro-inflammatory signals. They identified the lipid E1 (RvE1) in studies of the effects of aspirin in inflammation. They also concluded that inflammatory exudates from mice treated with aspirin had derivatives of EPA (essential fatty acid enriched in oils of fish and marine mammals) which include the product RvE1. These products had anti-inflammatory properties that had been synthesized in a two-step process requiring 5-LOX (5-lipoxygenase) and COX-2 (cyclooxygenase). Researchers also found that RvE1 resolves inflammation by suppressing the activation of NF-kB and the resulting synthesis of cytokines and chemokines. Serhan et al[2] extended their observations to an animal model in which the mice had severe inflammatory bowel disease induced by exposure to TNBS (2, 4, 6-trinitrorbenzene sulfonic acid). Pretreatment of the mice with RvE1 resulted in lower mortality, decreased weight loss, and less inflammation. Overall, the fish oil diet works because it results in the constant synthesis of anti-inflammatory products such as RvE1, and the 5-LOX inhibitor does not help the disease because it blocks the synthesis of such anti-inflammatory compounds. This study of RvE1 in inflammation demonstrates the importance of the endogenous mechanisms by which inflammation is controlled and the possibility of manipulating those endogenous mechanisms to treat or prevent inflammatory diseases.

1. Prescott SM, Stenson WF. Fish oil fix. Nature Medicine 2005;11:596-598.
2. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel Functional Sets of Lipid-derived Mediators with Antiinflammatory Actions Generated from Omega-3 Fatty Acids via Cyclooxygenase 2-Nonsteroidal Antiinflammatory Drugs and Transcellular Processing. J. Exp. Med 2000;192:1197-1204.