FUNCTIONAL MEDICINE UPDATE
AUGUST 2007
ISSN 1092-1761
Vol. 27, No. 8

Functional Somatic Syndromes

Functional somatic syndromes (FSS) are characterized by patterns of persistent bodily complaints for which adequate examination does not reveal sufficient explanatory or other specified pathology. These syndromes can be differentiated into three main types of bodily complaints: pain of different location (back, head, muscles or joints, abdomen, chest, etc.); functional disturbance in different organ systems (e.g. palpitation, dizziness, constipation or diarrhea, movement, sensation); and complaints centering around fatigue and exhaustion. There is no objective criterion to decide whether a pattern of bodily complaints should be seen as a functional somatic syndrome; lists drawn up by different authors can reflect their particular backgrounds and views.

A German research group conducted a meta-analysis of the published literature and their findings were recently published in *The Lancet*. The terms they found to be most commonly associated with FSS include the following:

- Irritable bowel syndrome (IBS)
- Chronic fatigue syndrome (CFS)
- Fibromyalgia (FMS)
- Multiple chemical sensitivity
- Nonspecific chest pain
- Premenstrual syndrome
- Non-ulcer dyspepsia
- Repetitive strain injury
- Tension headache
- Temporomandibular joint disorder
- Atypical facial pain
- Hyperventilation syndrome
- Globus syndrome
- Sick building syndrome
- Chronic pelvic pain
- Chronic whiplash syndrome
- Chronic lyme disease
- Silicone breast implant effects
- Candiosis hypersensitivity
- Food “allergy”
- Gulf War syndrome
- Mitral valve prolapse
- Hypoglycemia
- Chronic low back pain
- Dizziness
- Interstitial cystitis

- Tinnitus
- Pseudoseizures
- Insomnia

Conceptually, the bodily symptoms used as diagnostic criteria (i.e. abdominal pain or fatigue) are not specific but overlap for many functional somatic syndromes. Many patients fulfill criteria for more than one syndrome. The establishment of valid and generally accepted diagnostic criteria and procedures across medical specialties is among the issues the authors of the article suggest for further research. REF #1

Dr. Bruce McEwen and the Neurophysiology of Stress
Allostasis—the ability to achieve stability through change—is critical to survival. In a classic review article published in the *New England Journal of Medicine*, Dr. Bruce McEwen, of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, discussed the long-term effect of the physiologic response to stress (referred to as allostatic load). Allostatic load is the wear and tear that results from chronic overactivity or underactivity of allostatic systems (the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the cardiovascular, metabolic, and immune systems that protect the body by responding to internal and external stress).

In his article article, Dr. McEwen cites the cardiovascular system and its links to obesity and hypertension as the best-studied system of allostasis and allostatic load. In one analysis, data from the MacArthur Studies of Successful Aging were used to assess eight measures of increased activity of allostatic systems between 1988 and 1991. During the three years of follow-up, people in a higher functioning group (with higher allostatic-load scores at base line) were more likely to have incident cardiovascular disease and were significantly more likely to have declines in cognitive and physical functioning. Among women in this group, increased cortisol secretion predicted a decline in memory.
REF #2

Neuroendocrine factors, the HPA Axis, Cardiovascular Health, and Stress
The main components of the stress system are the corticotrophin-releasing hormone (CRH) and locus ceruleus-norepinephrine (LC/NE)-autonomic systems and their peripheral effectors, the pituitary-adrenal axis, and the limbs of the autonomic system. The CRH and LC/NE systems stimulate arousal and attention, as well as the mesocorticolimbic dopaminergic system. Reciprocal interactions exist between the amygdala and the hippocampus and the stress system, which stimulates these elements and is regulating them. CRH plays an important role in inhibiting GnRH secretion during stress, while, via somatostatin, it also inhibits GH, TRH, and TSH secretion, suppressing, thus, the reproductive, growth, and thyroid functions. The end-hormones of the hypothalamus-pituitary-adrenal (HPA) axis, glucocorticoids, have multiple roles. They simultaneously inhibit the CRH, LC/NE, and β-endorphin systems and stimulate the mesocorticolimbic dopaminergic system and the CRH peptidergic central nucleus of the amygdala. The central nucleus of the amygdala is a stress-regulating region of the brain, along with the bed nucleus of the stria terminals and the thalamic paraventricular nucleus.
REF #3-4

The deleterious effects of chronic stress and depression on cardiovascular health are well documented, but the physiological pathways by which stress and depression exert their influence are incompletely understood. Psychosocial stress can elevate circulating concentrations of the proinflammatory cytokine interleukin-6 (IL-6), perhaps consequent upon the influence of catecholamines on IL-6 levels. Some data suggest that catecholamines stimulate IL-6 release from adipose tissue, while inhibiting that from immune cells. IL-6 in turn has stimulatory actions on the hypothalamus-pituitary-adrenal axis, increasing hypothalamic secretion CRH, and responsiveness both of anterior pituitary release of adrenocorticotrophic hormone (ACTH) and adrenal cortical secretion of cortisol. Because activation of the HPA axis is associated with central obesity, hypertension, and insulin resistance, IL-6 may play a role in the pathogenesis of coronary heart disease through a combination of autocrine, paracrine, and endocrine mechanisms. REF #5

A study published earlier this year in *Psychophysiology* was a joint effort between investigators at the University of California, San Diego, and the Department of General Internal Medicine at University Hospital in Bern, Switzerland. This study involved 108 healthy individuals, and the aim was to investigate whether depressed mood and chronic hassles and uplifts predicted levels of hemostasis and proinflammatory markers. D-Dimer, type-1 plasminogen activator inhibitor (PAI-1), IL-6, and soluble intercellular adhesion molecule-1 (sICAM-1) plasma levels were analyzed from fasting venous blood samples. Analyses suggested that increases in hassle frequency predicted elevated levels of sICAM ($p = .034$), and increases in hassle severity predicted elevated levels of D-Dimer ($p = .017$). Increases in uplift intensity predicted lower levels of PAI-1 ($p = .004$) as well as showed a trend for decreased IL-6 ($p = .069$). Depressed mood did not significantly predict any dependent variable. The findings suggest that for even relatively healthy persons, increased perceptions of hassles are independently associated with greater inflammation and hypercoagulability, whereas increased perceptions of uplifts are independently associated with decreased hypercoagulability. REF #6

The Combined Effect of Diet and Lifestyle Factors on All-cause Mortality and Cause-specific Mortality

Diet and lifestyle influence morbidity and mortality during the course of life. Dietary patterns and other modifiable lifestyle factors are associated with mortality from all causes, coronary heart disease (CHD), cardiovascular diseases (CVD), and cancer, but few studies had investigated these factors in combination until the Healthy Aging: a Longitudinal study in Europe (HALE) project. The advantages of this Europe-wide study involving individuals aged 70 to 90 years included its great diversity in dietary patterns and lifestyle factors, its prospective nature, its large sample size, and its measurements of many confounders. The main outcome measures used in this study were ten-year mortality from all causes, coronary heart disease, cardiovascular diseases, and cancer. When all analyses were complete, the study authors concluded that among individuals aged 70 to 90 years, adherence to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-causes and cause-specific mortality. REF #7

It was pointed out in an editorial that followed the publication of the above study that the findings added to a considerable body of previous studies with similar conclusions. In the course of their own research, the authors of the editorial found that adherence to similar healthful lifestyle practices was associated with an 83% reduction in the rate of coronary disease, a 91% reduction in diabetes in women, and a 71% reduction in colon cancer in men. In addition, in the Lyon Diet Heart Study, individuals with established coronary disease showed reductions of 79% in heart disease after just a few years of following the Mediterranean-type diet. Because the HALE project was unique in its focus on older persons and given the higher underlying death rates in older people, the editorial authors suggest that application of the results to younger populations would almost surely show greater benefit. REF #8

One such study that supports the beneficial nature of the Mediterranean Diet was conducted by Italian researchers and reported in the *Journal of the American Medical Association* in 2004. This was a randomized single-blind study conducted from June 2001 to January 2004 and involved 180 patients with metabolic syndrome. The investigators aimed to assess the effect of a Mediterranean-style diet on endothelial function and vascular inflammatory markers in this patient population. The results of this study showed that consumption of a Mediterranean-style diet was associated not only with improvement of endothelial function and a significant reduction of markers of systemic vascular inflammation, but also with a reduction in the number of the components of the syndrome. REF #9

The Efficacy of Adaptogens

Plant adaptogens are compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors. The beneficial effects of multi-dose administration of adaptogens are mainly associated with the HPA axis, while adaptogens that provide a rapid response mechanism are associated with another part of the stress system: the sympatho-adrenal-system (SAS).The use of stimulating drugs derived from plants such as Rhodiola rosea, Schizandra chinesis, and Eleutherococcus senticosus typically generate no side effects, unlike traditional stimulants that possess addiction, tolerance, and abuse potential and produce a negative effect on sleep structure. Dr. Bland discusses a review of the SAS-mediated stimulating effects of single dose adaptogens that was published in *Phytotherapy Research*. REF #10

Curcuma longa has been used in China to effectively manage stress and depression-related disorders. Curcumin is the active component of curcuma longa. In mouse models, a group of Chinese researchers were able to demonstrate the antidepressant effects of curcumin. This same group has now studied whether curcumin may also alleviate stress-induced depressive-like behaviors and HPA axis dysfunction. The findings of this study were reported in Brain Research in 2006. REF #11

Persistent Organic Pollutants, Insulin Resistance, and Diabetes

A number of articles by a Korean research group led by Dr. DH Lee have been published in *Diabetes Care*. This group has studied associations between serum concentrations of

persistent organic pollutants (POPs) and insulin resistance and diabetes using data from the National Health and Nutrition Examination Survey (1999-2002). Earlier this year in Clinical Chemistry, more work from this group was published, this time demonstrating a strong interaction between serum γ-glutamyltransferase (GGT) with the prevalence of type 2 diabetes. REF #12-14

Clinician/Researcher of the Month

Sonia Lupien, PhD
Director, Laboratory of Human Stress Research
McGill University/Douglas Hospital Research Center
6875 Bld. Lasalle
Verdun, Quebec H4H 1R3
Canada
sonia.lupien@mcgill.ca
www.douglas.qc.ca/stress

Dr. Sonia Lupien is the Founder and Director of the Centre for Studies on Human Stress at the Douglas Hospital in Montreal, Canada, and is a scientist affiliated with the Department of Psychiatry at McGill University. She leads the Laboratory of Human Stress Research that specializes in measuring the acute and chronic impact of stress hormones on learning and memory in human populations. Dr. Lupien's projects include a research program on detection and intervention for stress in the workplace and the "DeStress for Success" Program that aims at educating children and teenagers on stress and its impact on learning and memory. She is also involved in the development of an interactive website providing useful tools for educators, healthcare practitioners, scientists, and the public: www.douglas.qc.ca/stress.

Dr. Bland and Dr. Lupien have a lengthy discussion about the origins of stress research and the challenges clinicians face in treating patients. Special attention is given to a program Dr. Lupien has developed called NUTS. NUTS is an acronym for the four characteristics of a stressor: Novelty, Unpredictability, Threat (to the ego or personality), and Sense (of control, which is diminished).

Heart Rate Variability

A growing body of literature has documented that job stress is associated with the development of cardiovascular disease. Obesity, insulin resistance, metabolic syndrome, and oxidative stress have also been linked to increased risk of cardiovascular events. Dr. Bland concludes this issue with a discussion of several articles pertaining to research on heart rate variability (HRV), a measurement he suggest may be a very important predictor of later-stage vascular and neuroendocrineimmune dysfunction. REF #15-18

References

1. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. *Lancet*. 2007;369:946-955.

2. McEwen BS. Protective and damaging effects of stress mediators. *New Engl J Med*. 1998;338(3):171-179.
3. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res*. 2002;53(4):865-871.
4. Fenoglio KA, Chen Y, Baram TZ. Neuroplasticity of the hypothalamic-pituitary-adrenal axis early in life requires recurrent recruitment of stress-regulating brain regions. *J Neurosci*. 2006;26(9):2434-2442.
5. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis*. 2000;148(2):209-214.
6. Jain S, Mills PJ, Von Kanel R, Hong S, Dimsdale JE. Effects of perceived stress and uplifts on inflammation and coagulability. *Psychophysiology*. 2007;44(1):154-160.
7. Knoops K, de Groot L, Kromhout D, Perrin AE, Moreiras-Varela O, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and Women: the HALE project. *JAMA*. 2004;292(12):1433-1439.
8. Rimm EB, Stampfer MJ. Diet, lifestyle, and longevity—the next steps? *JAMA*. 2007;292(12):1490-1492.
9. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome. *JAMA*. 2004;292(12):1440-1446.
10. Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. *Phytother Res*. 2005;19(10):819-838.
11. Xu Y, Ku B, Tie L, Yao H, Jiang W, et al. Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB. *Brain Res*. 2006;1122:56-64.
12. Lee DH, Lee IK, Jin SH, Steffes M, Jacobs DR. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults. *Diabetes Care*. 2007;30(3):622-628.
13. Lee DH, Lee IK, Song K, Steffes M, Toscano W, et al. A stong dose-response relation between serum concentrations of persistent organic pollutants and diabetes. *Diabetes Care*. 2006;29(7):1638-1644.
14. Lim JS, Lee DH, Park JY, Jin SH, Jacobs DR. A strong interaction between serum γ-glutamyltransferase and obesity on the risk of prevalent type 2 diabetes: results from the third national health and nutrition examination survey. *Clinical Chem*. 2007;53(6):1092-1098.
15. Kang MG, Koh SB, Cha BS, Park JK, Woo JM, et al. Association between job stress on heart rate variability and metabolic syndrome in shipyard male workers. *Yonsei Med J*;45(5):838-846.
16. Liao D, Sloan RP, Cascio WE, Folsom AR, Liese AD, et al. Multiple metabolic syndrome is associated with lower heart rate variability. *Diabetes Care*. 1998;21(2)2116-2122.
17. Laaksonen DE, Laitinen T, Schonberg J, Rissanen A, Niskanen LK. Weight loss and weight maintenance, ambulatory blood pressure and cardiac autonomic tone in obese persons with the metabolic syndrome. *J Hypertens*. 2003;21(2):371-378.

18. Park SK, Schwartz J, Weisskopf M, Sparrow D, Vokonas PS, et al. Low-level lead exposure, metabolic syndrome, and heart rate variability: the VA normative aging study. *Environ Health Perspect*. 2006;114(11):1718-1724.