Gut–Brain: Major Depressive Disorder, Hypothalamic Dysfunction, and High Calcium Score Associated With Leaky Gut

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Tom, a 52-year-old male, arrived in my office with chief complaint of depression, chronic fatigue, fibromyalgia, and low libido. Tom is a successful business man with a string of lucrative stores. His psychiatrist prescribes 2 different antidepressant drugs, a selective serotonin reuptake inhibitor (SSRI) drug and lithium carbonate. His cardiologist prescribes lisinopril for hypertension. Despite treatment, Tom complains of continued symptoms of depression, chronic fatigue, vague body aches, pains, and arthritis.

HYPOTHALAMIC DYSFUNCTION FROM LEAKY GUT

Tom also complains of abdominal gas and bloating, especially after meals. His fecal stool antigliadin immunoglobulin A (IgA) antibody was markedly elevated (343 units with normal < 10 units). He had multiple other food sensitivities to egg, milk, and soy protein. A lactulose-mannitol intestinal permeability test was abnormal. A diagnosis of wheat gluten sensitivity and leaky gut syndrome was made, and Tom started his gluten-free diet.

Tom had low testosterone (263 ng/dL total) and low luteinizing hormone/follicle-stimulating hormone (LH/FSH) as well, suggesting hypothalamic dysfunction. Tom was given a clomiphene stimulation test. Following the 6-week daily administration of 25 mg of clomiphene (oral tablet), Tom reported improved libido and energy. His serum LH increased from 2.5 to 9.7 mIU/mL, and serum testosterone increased from 263 to 543 ng/dL. Tom found he could taper off one of the antidepressants (the lithium) and reduced his SSRI drug dosage. A computerized tomography (CT) scan calcium score showed elevated calcium score of 490 (95th percentile) indicating significant atherosclerotic plaque and high risk for heart disease. Tom's cardiologist started him on atorvastatin, a statin anticholesterol drug, and a follow-up cholesterol on the statin was 125 mg/dL.

CENTRAL HYPOTHYROIDISM AND HYPOTHALAMIC DYSFUNCTION

Tom's thyroid labs suggested central hypothyroidism, a core feature of chronic fatigue, and fibromyalgia described by Drs Holtorf and Teitelbaum.[1-3] Tom's thyroid-stimulating hormone (TSH) was in the low normal range (0.9 mIU/L); however, the free T_3 and free T_4 were also in the low end of the range (2.3 pg/mL and 0.8 ng/dL). After 6 weeks of treatment with natural desiccated thyroid (1 grain tablet daily), repeat labs showed improvement. The TSH was suppressed 0.04, and the free T_3 and T_4 had risen to the upper end of the normal range (4.1 pg/mL/1.6 ng/dL). Although low cortisol is a common feature of chronic fatigue syndrome, Tom's serum cortisol was normal, so hydrocortisone was not given.

My Diagnosis

My diagnosis was as follows: Severe gluten sensitivity with leaky gut, lipopolysaccharide (LPS)-induced depression, chronic fatigue, fibromyalgia, central hypothyroidism and hypogonadism with hypothalamic dysfunction responsive to clomiphene stimulation, and LPS-induced coronary atherosclerosis.

CLOMIPHENE BLOCKS HYPOTHALAMIC ESTROGEN RECEPTORS AND UP-REGULATES THE HPA

Clomiphene, Food and Drug Administration (FDA) approved as a fertility drug for women, is considered "off label use" when prescribed to males. Clomiphene blocks the hypothalamic estrogen receptor, thus upregulating the hypothalamic-pituitary-adrenal (HPA) axis, increasing LH and FSH, and increasing testosterone.[4] Clomiphene preserves fertility, unlike exogenous testosterone, which suppresses LH/FSH and impairs fertility.[5-9]

HYPOTHALAMIC CONTROL OF TESTOSTERONE BY ESTROGEN RECEPTORS

How does clomiphene work? A 2006 report in the *European Journal of Endocrinology* by Dr Rochira from Italy is illustrative.[5] Dr Rochira studied 2 males with genetic deficiency in the aromatase enzyme, who had virtually no circulating estrogen. When these 2 males were given topical estrogen, this decreased gonadotropin releasing hormone, suppressed LH and FSH, and suppressed testosterone.[5] This elegant study shows how estrogen stimulation of hypothalamic receptors suppresses LH/FSH as well as testosterone production in males. Clomiphene blocks hypothalamic estrogen receptors, increasing testosterone production.

IRREVERSIBLE HYPOTHALAMIC DAMAGE

Tom's excellent response to clomiphene indicated his hypothalamic dysfunction is indeed reversible and has a good prognosis with treatment. If the patient fails to respond to clomiphene, then irreversible hypothalamic damage is likely, usually from toxins or psychoactive drugs. For example, animal studies using psychoactive drugs such as paroxetine, sertraline, amphetamines, and 3,4-methylenedioxy-methamphetamine (MDMA) show similar irreversible damage to serotonergic axons and nerve terminals, especially the fine fibers arising from the dorsal raphe nucleus which supply serotonin to the brain.[10] Dr Bauman says, "High-dose administration of SSRIs (antidepressants) produces swollen, fragmented, and abnormal 5-HT (5-hyroxy-tryptophan) terminals, which are indistinguishable from the effects of MDMA and other substituted amphetamines."[10] My clinical experience is in agreement having seen patients with irreversible hypothalamic dysfunction after long-term SSRI antidepressant, amphetamine, benzodiazepine, or MDMA use, singly or in combination. These patients have irreversible hypothalamic dysfunction and usually require exogenous testosterone, thyroid, and hydrocortisone.[1-3]

A NASTY COMBINATION OF PPIS AND SSRIS

The combination of proton pump inhibitor (PPI) antacids and SSRI antidepressants (omeprazole and venlafaxine) is particularly damaging. Omeprazole, a PPI, effectively turns off gastric acid production. Long-term use of PPI drugs is associated with adverse effects of gut dysbiosis; malabsorption of vitamin B_{12}, calcium, iron, and magnesium; and *Clostridium difficile* enterocolitis, pneumonia, and osteoporotic fracture.[11-12] These adverse effects are bad enough. Even worse is the inhibition of cytochrome P450 enzyme system, reducing clearance of SSRI antidepressants by 20% to 40%, potentiating the effect of the drug.[13] One such young male on this drug combination was found to have a testosterone level of 47 ng/dL, the lowest I have ever seen, and no doubt a victim of drug-induced damage to the serotoninergic axons in the hypothalamus. Another common adverse side effect of SSRI drugs is loss of sexual function, which may persist for years after stopping the drug.[14-16] Again, I suspect this is caused by damage to brain stem nuclei. Perhaps future animal studies will clarify this anatomical defect.

LEAKY GUT, LPS CAUSES MICROGLIA ACTIVATION IN THE BRAIN

As recent work by Allesio Fasano has revealed, in susceptible individuals, the ingestion of wheat gluten triggers the release of zonulin, a hormone that opens the "tight junctions" between epithelial cells of the gastrointestinal (GI) mucosa.[17-20] For people with gluten sensitivity, the prolonged opening of channels between the epithelial cells makes the gut lining permeable to undigested food particles and gut bacteria, which "leak" into the blood stream; thus, we have a leaky gut. This is also called low-level endotoxemia, or LPS, the outer membrane of enteric gram-negative bacteria that activates macrophages and immune cells to release of inflammatory cytokines into the blood stream. This slurry of LPS and inflammatory mediators eventually reaches the cerebral circulation, causing inflammation in the brain with activation of microglia, disturbance of the autonomic nervous system and neurotransmitter production causing depression, chronic fatigue, autonomic dysfunction and other disorders.[21-37]

LPS, ENDOTOXEMIA, MAJOR DEPRESSION, AND ATHEROSCLEROSIS

Michael Maes and others have found elevated antibodies to LPS (enteric gram-negative organisms) in patients with major depression disorder, chronic fatigue, and fibromyalgia. Patient improvement correlates with decreasing LPS antibody levels. Perhaps this explains why depression is frequently refractory to SSRI drugs. If the etiology is microglial activation and brain inflammation triggered by circulating LPS with low-level endotoxemia, as proposed by Michael Maes and others, then SSRI drugs are not addressing the underlying cause, which is LPS activation of toll receptors in glial cells with upregulation of nuclear factor κB (NF-κB).[38-49]

Because depression and coronary artery disease may share a common pathway, one might ask if there is an association. Major depressive disorder is associated with an 80% to 200% increased risk of death from coronary heart disease, depending on the study cited.[50-52] Indeed, antidepressant drug use is common among patients with coronary artery disease. Women with history of antidepressant use had 334% greater risk of sudden cardiac death in the Nurse's Health Study.[52]

One might ask whether there is a shared etiology between depression and atherosclerotic vascular disease. The 2 entities are both caused by translocated LPS-induced inflammation. Indeed endotoxemia has been considered as an etiology of atherosclerotic disease.[53] Dr Wiederman from Italy found that subjects with circulating (LPS) endotoxin levels greater than 50 pg/mL had a 3-fold greater risk of cardiovascular disease, compared with those under 50 pg/m.[54] The toll receptor is the pattern recognition receptor on the macrophage membrane surface, which identifies the LPS and triggers NF-κB

activation, a transcription gene for inflammatory cytokines in both the brain and endothelium. Blocking this receptor might be a logical treatment to prevent heart disease. This has been done in a genetically modified mouse model. Elegant studies reveal a 60% reduction in atherosclerosis in mice lacking the toll receptor or its downstream signaling molecule MyD88.[55] Atherosclerotic disease in dialysis patients is directly related to LPS-induced endotoxemia.[56-58]

ATHEROSCLEROTIC PLAQUE AS INFECTED BIOFILM

In his 1908 *Textbook of Medicine*, Sir William Osler speculated that atherosclerotic plaque was caused by infection. Over the years, Osler's textbook gathered dust while the cholesterol theory prevailed, and statin drugs provided a new revenue stream for the drug industry. The idea that infection caused atherosclerosis was resurrected in the 1970s when herpes virus was found to induce atherosclerotic lesions in chickens identical to those in humans.[58] Interest again surged in 1993 when Dr Kuo reported chlamydia infection in atherosclerotic plaque material from autopsies.[59] More recently, working independently, Drs Stephen Fry, Bernard Lanter, Stephan Ott, and Omry Koren examined atherosclerotic plaque obtained from surgical specimens using 16S rRNA cloning techniques. Quite remarkably, they all found atherosclerotic plaque is biofilm colonized by multiple bacterial, fungal, and protozoal organisms.[60-64]

CHOLESTEROL THEORY HAS BEEN FALSIFIED

Current accepted dogma proposes cholesterol as the cause of atherosclerotic plaque, and, therefore, reduction of serum cholesterol with a statin drug should prevent coronary artery disease. Quite to the contrary, the cholesterol theory has been falsified. According to Dr William R. Ware, there is no correlation between serum cholesterol and the amount of atherosclerotic plaque when reviewing either autopsy studies or coronary calcium score studies.[65] The lack of relationship between serum cholesterol and calcium score was reported by Dr Hecht: "There were no significant differences in the calcium scores throughout the entire range of all lipid parameters; calcium percentiles were virtually identical within lipid value subgroups."[66] Drs Ravnskov and McCully concur with Drs Ware and Hecht.[67,68] A dozen studies show low cholesterol in the elderly is a marker for increased mortality, not improved survival. Also, in selected medical conditions such as congestive heart failure, haemodialysis, chronic obstructive pulmonary disease, as in the elderly, higher cholesterol is associated with improved survival and lower cholesterol with increased mortality.[69]

THE ENDOTOXIN-LIPOPROTEIN HYPOTHESIS

A low-serum cholesterol is problematic for another reason. Cholesterol is part of our immune defense system. Both animal and human studies show cholesterol inactivates LPS and bacterial endotoxin, serving as a second line of defense against translocated LPS.[70,71] The ability of cholesterol to detoxify LPS is explained by Dr Sandek as the "endotoxin-lipoprotein hypothesis."[69] Dr Pajkrt studied this hypothesis in-vivo with human volunteers, infusing reconstituted HDL cholesterol just prior to endotoxin infusion. The authors concluded the HDL cholesterol infusion "dramatically reduced the endotoxin-induced inflammatory response, reduced inflammatory cytokines, cell activation, and clinical symptoms in humans … partly caused by neutralization of endotoxin by reconstituted HDL cholesterol."[70] As one might expect, low HDL cholesterol level is a predictor of increased mortality in patients with endotoxemia from sepsis.[72]

STATINS FAIL FOR CALCIUM SCORE

Getting back to our patient's elevated calcium score treatment with a statin drug to reduce cholesterol, one might ask the question, even though the statin drug is effective for reducing cholesterol, how effective are statins for reducing calcium score? Randomized trials using statin drugs to treat calcium score have been disappointing.[73,74] Dr Gill summarizes the studies:

> As of 2010 there had been five randomized controlled studies showing that statin drug treatment does not reduce coronary calcium score. Worse, the statin treatment showed progression of coronary calcium score indistinguishable from the nontreated placebo group."[75]

AGED GARLIC TREATS CALCIUM SCORE

Because statin drugs have been a failure for treating calcium score, is there an alternative? The answer comes from Matthew J, Budoff, MD, an early pioneer of the calcium score as a surrogate marker for coronary plaque. Dr Budoff explored the use of aged garlic for elevated calcium score in 3 randomized, placebo-controlled trials. The aged garlic was far more effective than the statin drug, reducing the progression of calcium score by 60% to 70% compared with controls, a remarkable finding.[76-78]

MECHANISM FOR AGED GARLIC PROTECTION FROM ATHEROSCLEROSIS

The mechanism by which garlic confers protection from atherosclerosis was studied in genetically modified mice by Dr Ayelet Gonen. Daily garlic (allicin) reduced the atherosclerotic plaque area by 70% in apolipoprotein E (ApoE)-deficient mice, and by 60% in low-density lipoprotein (LDL) receptor knockout mice. Additional studies showed the possible mechanism of protection. Garlic (allicin) binds to the LDL particle and prevents LDL oxidation, thus inhibiting macrophage uptake and degradation of LDL.[79]

ATHEROSCLEROTIC PLAQUE AS PSEUDOMONAS INFECTED BIOFILM

If atherosclerotic plaque is an infected biofilm, perhaps the antimicrobial activity of aged garlic could represent another mechanism for garlic's benefits in retarding calcium score progression. Dr Bernard Lanter identified pseudomonas

16S rRNA genes in 6 of 15 atherosclerotic plaque specimens.[61] Dr Omry Koren found *Pseudomonas* (*Chryseomonas*) in all (100%) plaque specimens examined.[64] Garlic is antimicrobial and is effective against *Pseudomonas* biofilm, inhibiting quorum sensing and virulence.[80,81] Dr Lihua's group showed, "Allicin disturbed formation and maturation of *Pseudomaonas* biofilm."[82] As mentioned above, plaque harbors a diverse biofilm colony of bacterial, fungal, and protozoal organisms. If so, then perhaps a synergistic combination of additional botanicals such as garlic, berberine, and boswellia would be more effective. Unresolved questions relate to the timing of the plaque infection. When does the infection occur in the life cycle of plaque formation? Is infection an initiating feature, or does infection occur later, after the plaque has already formed? These and other questions await further study.

BERBERINE, ANTIDOTE FOR LEAKY GUT EPIDEMIC

A state of low-level endotoxemia has been implicated in the increasing incidence of celiac disease, inflammatory bowel disease, and intestinal infection.[83,84] Treatment of leaky gut and low-level endotoxemia involves elimination of nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs, alcohol, wheat gluten, other reactive foods, and pesticides from the diet. Probiotics, digestive enzymes, fiber, glutamine, colostrum, and zinc are frequently found useful for the leaky gut patient.[85-88] Although berberine acts as an antidiabetic agent similar to metformin with upregulation of AMP kinase, berberine has may other benefits and may represent our "antidote for an epidemic."[89-90] Berberine actually closes down the tight junctions in the gut epithelial cells.[91] Berberine has anti-inflammatory activity, downregulating proinflammatory genes in macrophages such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), and others.[92] Berberine has antiendotoxin effects by blocking the toll receptors in LPS-treated mice. Dr Chu concludes: "With the advantage of lower cost, faster curative effect, and little side effect, berberine, the newly-discovered LPS antagonist, could be widely utilized as a substitute for expensive drugs in the treatment of LPS-induced diseases."[93] Berberine acts as a potent inhibitor of neuroinflammation via activation of AMP kinase signaling pathways in microglial cells, thus inhibiting NF-κB.[94,95] Other natural products that inhibit microglial activation are resveratrol, pterostilbene, and boswellia.[96-99] Berberine exerts antidepressant-like effects in various mouse models of depression by increasing neurotransmitter levels in the brain. Dr Kulkarni found berberine "increased levels of norepinephrine (31%), serotonin (47%) and dopamine (31%) in the whole brain."[100] Berberine is effective for acute diarrhea, inhibits biofilm formation, and demonstrates remarkable antimicrobial activity against chlamydia, methicillin-resistant *Staphylococcus* aureus (MERSA), and other microorganisms.[101] Berberine inhibits atherosclerosis in genetically modified mice.[102] Berberine is useful for congestive heart failure and cardiomyopathy by increasing the ejection fraction and preventing arrhythmia.[103,104]

CONCLUSION

Low-level endotoxemia from leaky gut has received considerable attention as an etiologic factor for many of our modern diseases. The case report highlighted in this article illustrates a patient with depression, hypothalamic dysfunction, endocrinopathy, atherosclerotic vascular disease, and hypertension, perhaps all caused by a shared etiology: leaky gut with low-level endotoxemia.

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