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Are the estrogenic hormonal effects of environmental toxins affecting small intestinal bacterial and microfilaria overgrowth?

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A B S T R A C T

The important role of microfilaria (worms) in human and animal disease remains an area of key disagreement between the naturopathic and allopathic physicians. While microfilaria infections are rampart in undeveloped countries, they rarely rise to identification as a cause of disease in Western countries. New research studies in the diagnosis and treatment of SIBO (Small Intestinal Bacterial Overgrowth) and (IBD) Inflammatory Bowel Diseases of ulcerative colitis, Crohn's Disease and microcytic colitis may make both sides equally correct. A study of rifaximin failures in SIBO positive individuals finds biomarkers of decreased Free Androgen Index (FAI), high incidence of autoimmune disease and elevated Sex Hormone Binding Globulin (SHBG). The author hypothesizes that the underlying pathophysiology is increased exposure to Endocrine Disrupting Chemicals (EDCs) which hormonally act as xeno-estrogens. These xeno-estrogens increase the host production of SHBG, reduce pituitary stimulation of androgen product and result in a shift to estrogen dominance. Estrogen dominance is associated with autoimmune diseases and catabolic states. Treatment with a mixture of anabolic steroids that raises the FAI and lowers SHBG results in dramatic improvement in the signs and symptoms and recovery of the vast percentage of severe SIBO sufferers the author has treated. Similar results have been seen in severe pre-surgical cases of IBD whom fail all pharmaceutical interventions. Based on the recent recognition of the biological importance of Wolbachia in the occurrence of major diseases in the underdeveloped countries such as onchocerciasis, and the sexual nature of Wolbachia's role in helminths reproduction, the author hypothesizes that the EDCs are shifting the host's hormonal milieu in a more estrogenic direction and increasing reproduction of helminths changing the gastrointestinal microbiota. Present allopathic treatment of onchocerciasis utilizes albendazole and avermectin as therapy against the microfilaria larvae and doxycycline as bactericidal for Wolbachia. The allopathic treatments are unacceptable for pregnancy and children. Both naturopathic and allopathic treatments share a common focus on the suppression of the underlying bacterium Wolbachia infestation. The author hypothesizes that treatment of these two very different gastrointestinal diseases involves first establishing a normal, anabolic hormonal milieu and concurrently controlling an underlying yet unrecognized microfilaria overgrowth through naturopathic and allopathic treatments prescribed to the host. A case report of one such critically ill individual is noted. A thorough case controlled observation of symptoms matched with biological culture colony count and concentration of microfilaria in disease before and after the aforementioned anabolic treatment may answer the hypothesis.

Introduction/background

Microfilaria [1] refers to a "pre-larvae or advanced embryo" stage that exists prior to the first larva stage of certain parasitic nematodes/helminiths of the family Onchocercidae. While the adults live in a tissue or circulatory system of vertebrates (animals), the microfilariae are released into the blood stream where they migrate to just below the skin. Intact microfilaria can be sucked up intact into the mosquito (arthropod) with the bite, and subsequently enter the mosquito's circulation. Here they mature to the first stage larvae. This vector continues with the mosquito biting another vertebrate animal.

In the tissue-dwelling species, the eggs hatch in the uterus of the female and unsheathed microfilariae are released. In most blood-dwelling species, the microfilariae release embryonic eggs that are sheathed in the envelope of the egg. They are 'hatched' or ex-sheathed in the arthropod vector. In some species of Onchocercidae, the release of microfilariae by the adult female is periodic—occurring at a particular time of the day or night to increase chance of being picked up by

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the blood-feeding arthropod vector.

The Wolbachia is a more primitive bacterial life-form than the parasitic nematode. The nematodes (parasitic worms) not only contain significant amounts of Wolbachia, but also the nematodes through transovarially transmission moves the bacteria from the adult female uterus to the offspring [2]. The discoverers have identified the potential importance of these bacteria:

(1) Bacteria-derived molecules should be considered as having an immunological and pathological role in filarial disease, as the nematodes are able to survive in immune competent hosts and
   a. Wolbachia [2] manipulate of mast cell-mediated vasodilation to enhance infectivity of vector-borne larvae.
   b. Wolbachia [2] is the principal driver of innate and adaptive Th1 inflammatory immunity which contributes to disease and enhanced infectivity.
   c. Wolbachia inserts a genome fragment into the host X chromosome necessary for female nematode fertility [3]. The failure to do so leaves the nematode a male that grows and dies without reproducing.
(2) As the Wolbachia bacteria are needed by the host nematode, they represent a target for therapy. It has been well known for more than 30 years that tetracycline, which kills intracellular bacteria, such as Wolbachia, also kills the nematodes Brugia pahangi and Litomosoides sigmodontis [4]. When doxycycline and ivermectin were used together, doxycycline (DOXY) dose: 10 mg/kg/day and ivermectin (IVM): 6 microgram/kg orally weekly, the resultant loss of both Wolbachia and nematoid DNA were similar to those of control worms, suggesting a loss of both Wolbachia and nematodes. Electron microscopy of nematodes recovered from the IVM/DOXY combination group showed complete loss of uterine content in females and immunohistochemistry for Wolchachia was negative [5].
(3) The Wolbachia bacteria is necessary for the reproduction of the Onchocerca. Death and clearance of the Wolbachia after tetracycline treatment causes reproductive abnormalities in worms and affects worm's embryogenesis, resulting in sterility [6].

Five prescription medications have been clinically tested for treatment of Onchocerciasis.

1. Anti-rickettsia: erythromycin and doxycycline. Chloramphenicol is less effective.
2. Anti-parasitic: ivermectin, abendazole and diethylcarbamazine

(4) WALADin benzimidazoles modulate the function of prophobilinogen synthases orthologs. These medications have emerged as species-selective PBGS inhibitors against Wolbachia endobacteria of filarial worms. However, the medications may result in inhibition or stimulation of Pseudomonas aeruginosa depending on facts and pH [7]. This implies that Wolbachia is linked to survival/proliferation of Pseudomonas and other bacteria as well. Pseudomonas is implicated in the water of individuals at high risk for inflammatory bowel disease [8].
(5) While tetracycline as anti-Wolbachia therapy delivers safe macrofilaricidal activity and superior therapeutic outcomes compared to all standard antifilarial treatments, this therapy is contraindicated in children under 8 years of age and pregnancy [9].

Therefore, the primary goal of the anti-Wolbachia consortium is to find drugs and regimens that reduce the period of treatment from weeks to 7 days or less and find drugs which would be safe in exclude target populations (children and pregnancy) [9].

Therefore, the goal of any treatment that destroys the Wolbachia or shifts the gender-preference from female to male of the Onchocerca proves to reduce the number of Onchocerca and improve the vertebral host health status akin to the present treatment for Onchocerca, river blindness. The potential drop in the concentration of the microfilaria in the microbiota by changing to a more androgenic milieu potentially changes the makeup of the gastro-intestinal microbiota and may correlate to symptom relief.

Turner [10] reported in a double-blind, in randomized field trial of 6 weeks of group (1) doxycycline 200 mg/day alone or in combination with ivermectin 150 mcg/kg/day or (group 2) placebo or ivermectin alone at four months. The combination treatment of doxycycline/ivermectin had lower levels of microfilaridermia and high frequency of amicrofilaridermia compared with ivermectin or doxycycline only groups. At 12 months, 89% of the doxycycline/ivermectin group and 67% of the doxycycline only group were amicrofilaridermic, compared with 21% of the ivermectin only group [10]. Of strong note, O. volvulus were completely depleted of Wolbachia and all embryonic stages in utero in the doxycycline group [10] and the sterilization was unaffected by ivermectin [10].

Gayen [11] in a placebo controlled field trial established that the combination of doxycycline/(DOXY) (200 mg/day) and albendazole (ABZ): 400 mg/day provided the best efficacy by totally eliminating the circulating microfilaria (in 42% cases) on day 365 with (99.85%, $P < .05$) suppression; better than DOXY (69%, $P < .05$) and ABZ (89% $P < .05$). Gayen concluded "a 30-day course of doxycycline and ABZ in combination is a safe and well-tolerated treatment for lymphatic filariasis with significant activity against microfilaremia" [11].

Tafatatha [12] noted that doubling the standard dosage of ivermectin (IVM) and albendazole (ABZ) did not improve clearance rate of microfilaria based on count/ml [12].

Kar [13] noted the higher and or more frequent dosing with ABZ with a fixed 300 mg dose of diethylcarbazine resulted in only marginally greater clearance of lymphatic filariasis [13].

Kramer [14] noted that in dogs with lung pathology from Dirofilaria immitis, that the combination of doxycycline/DOXY (20 mg/kg per os daily) with ivermectin/IVM (6mcg/kg per os) for 24 weeks resulted in less severe arterial lesions and virtual absence of thrombi after intramuscular injection of melarsomine dihydrochloride at week 12 [14].

SIBO observation

In light of known and published information comes a quandary of gastro-intestinal symptoms labelled Small Intestinal Bacterial Overgrowth Syndrome [15]. The symptom complex includes bloating, diarrhea, malabsorption, weight loss and malnutrition. Some diagnostic studies have confirmed a high concentration of colon bacteria in the small bowel/jejunum. Some breathe testing of hydrogen/methane after lactulose and glucose may be positive in a significant percentage of sufferers. The prognosis can be quite serious. The patients may appear suffering from extremely mal-nutrition and cachexia.

Under normal physiological circumstances, there are several endogenous defense mechanisms for preventing bacterial overgrowth: gastric acid secretion, intestinal motility, intact ileocecal valve, immunoglobulins within intestinal secretion and bacteriostatic properties of pancreatic and biliary secretion.

Human intestinal microbiota creates a complex polymicrobial ecology. This is characterized by its high population density, wide diversity and complexity of interaction. Any imbalance of this complex intestinal microbiome, both qualitative and quantitative, might have serious health consequence for a macro-organism, including small intestinal bacterial overgrowth syndrome (SIBO). SIBO is defined as an increase in the number and/or alteration in the type of bacteria in the upper gastrointestinal tract. There are several endogenous defense mechanisms for preventing bacterial overgrowth: gastric acid secretion, intestinal motility, intact ileo-caecal valve, immunoglobulins within intestinal secretion and bacteriostatic properties of pancreatic and biliary secretion. Etiology of SIBO is usually complex, associated with disorders of protective antibacterial mechanisms (e.g. achlorhydria, pancreatic exocrine insufficiency, immunodeficiency syndromes), anatomical abnormalities (e.g. small intestinal obstruction, diverticula,