RESEARCH ARTICLE

Environmental Exposures as a Potential Underlying Factor in Chronic Fatigue Syndrome; a Case Report

An Environmental Medicine perspective on a complex syndrome; Could toxic exposures be the cause?

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ABSTRACT: The current standard of care medical model is a disease-based approach, focused on achieving a specific diagnosis and applying a monotherapy to the labeled condition. Chronic fatigue syndrome (CFS), not dissimilar to other complex syndromes may require a different viewpoint to improve patient outcomes. This model that would be adequately suited for complex conditions must intervene at multiple levels to address core clinical imbalances. In these syndromes, diagnosis and determination of appropriate treatment options is a complex process that requires a move toward a more patient-centric model of care. One that includes elucidation of potential causes, such an ongoing environmental exposures, involves patient participation and provides individualized care. The functional medicine model is uniquely suited to more fully evaluate and understand underlying factors in multifaceted syndromes such as CFS. Functional medicine practitioners spend time with their patients, listening to their histories and looking at the interactions among genetic, environmental, and lifestyle factors that can influence long-term health and disease progression. This model goes beyond the diagnosis, and focuses on an understanding of the distinct mechanisms including predisposing genetic factors, unique environmental susceptibilities and underlying dysfunctions in order to determine and avoid hazardous toxic exposures and/or lifestyles, prescribe appropriate evidence based therapies all aimed to improve overall health and function over time.

Objectives: The purpose of this case study is to describe the potential benefits of a functional medicine approach, emphasizing genetic uniqueness and environmental exposures, in the development, progression and treatment of CFS.

Methods: A patient diagnosed with CFS was assessed using the functional medical model, with a focus on environmental exposures and genetic SNP profiles. Personalized care was provided, including education on environmental hazards and treatment. Outcome measures were obtained pre- and post-treatment. These measures included validated surveys (Medical Symptoms Questionnaire, Revised Fibromyalgia Impact Questionnaire and Chronic Fatigue-Fibromyalgia Questionnaire) and objective markers such as blood and salivary biomarkers of health and function.

Results: The patients had clinically significant reduction in fatigue, improved health and function as documented with both subjective and objective outcome measures, up to as much as 12 months after treatment initiation. Although some mild side effects were reported, no serious adverse effects occurred.

Conclusion: This unique case study suggests the functional medicine model with emphasis on environment-genetic interactions may be of benefit in the assessment and management of patients with complex syndromes such as CFS. Further investigations with larger studies, including randomized controlled trials, in a more specific CFS population (with known toxic hazardous exposures) may be warranted.

Keywords: Chronic pain; Chronic Fatigue Syndrome; Fibromyalgia Syndrome; Functional Medicine; Environmental Medicine

Introduction: Chronic Fatigue Syndrome (CFS), also known as Myalgic Encephalomeylitis, is a complex and debilitating chronic disease with a serious impact on one's quality of life. To date over 2 million people suffer from this condition.[i] Hallmark symptoms include extreme exhaustion, non-restorative sleep, cognitive impairment and post-exertional malaise. To date over 5000 articles appear in the peer reviewed literature, many of these focused on attempting to shed light on understanding the potential causes of this syndrome. Proposed mechanisms include viral infections, immune system dysfunction, altered HPA axis, hypoglycemic and hypotensive changes as well as peripheral neuropathies.[ii] One or many of these potential physiological dysfunctions may be manifesting in a single patient and the core underlying dysfunctions are likely unique to each case, but a cohort of these patients may be dealing with an environmental problem at the core of these dysfunctions. For example, environmental toxins could be a contributing factor in the immune dysfunction, as they have been implicated in a reduced capacity to fight infections, allergies and autoimmunity.[iiiiv] Toxins have also shown to cause peripheral neuropathies, suggesting further overlap.[vvi] In addition to the immune and neurological changes, many of the symptoms of CFS overlap with the symptoms of chronic toxic encephalopathy such as fatigue, lightheadedness, dizziness, insomnia, cognitive impairments such as brain fog, memory and learning problems and mood changes such as depression and irritability.[viiviiiix] Research suggests that many of these proposed mechanisms lead to one final common insult related to mitochondrial damage and oxidative stress.[x] Although, further toxicology data is needed, environmental xenobiotics including chlorinated pesticides, volatile solvents and heavy metals have also been suggested as both linked to CFS and mitochondrial damage.[xixii]

Our environment is rapidly changing. To date thousands of new, synthetic, toxicants have been added to the Agency for Toxic Substances and Disease Registry.[xiii] Many of these commonly found substances have been linked to central nervous system and mitochondrial damage as well as chemical-driven liver and kidney damage. These substances are ubiquitous and exposure is most certain. Route, length and extent of exposure will determine the total toxic load (bioaccumulation) in addition to a patient's distinct susceptibility via their biochemical individuality (produced by DNA alterations called single nucleotide polymorphisms – SNPs) which determines the functioning of detoxification pathways. Some people have high blood levels of particular toxins because of a poor ability to clear these compounds, even though exposure is no different from others.[xiv] Exposure examples include volatile solvents which are routinely used in

industrial processes to manufacture consumer products. Air and water pollution are common routes of exposure in both our homes and workplaces. Our population is also exposed by inhalation or ingestion of car exhaust, paints, glues, adhesives, and lacquer thinners. Solvents are used in large numbers to produce items in our homes such as furniture, building materials, paint, shoes, cleaning and degreasing agents, inks, pharmaceuticals, and as additives to gasoline. Toxicology data suggests that these toxins are known to contribute to fatigue, atrophy of skeletal muscles, muscle weakness, loss of coordination, vision problems, and depression of the central nervous system. These cases illustrate that the astute clinician should consider inquiring about a patient's current and past environmental history and family history, which may shed light on current or past harmful exposures and/or possible increased susceptibility to ambient exposure.

PATIENT CASE:

In 2016 R.M. a 62yo female was referred for Functional Medicine emphasizing an environmental exposure assessment. She has had numerous health concerns, fungal overgrowth, bacterial infections, parasite cleansing, pre-cancerous lesions, testing and treatment over the years, but unfortunately continued to experience a decline in her health.

Her symptoms started gradually between the age of 20-35 and were progressive since then. Symptoms include severe fatigue (diagnosed as CFS), poor concentration, mild memory loss & brain fog, depression, dizziness, insomnia, skin rashes, severe muscle and joint pain (diagnosed as Fibromyalgia and arthritis), extreme multiple chemical sensitivity (MCS), electro hyper sensitivity (EHS, developed late 30's, after MCS), weight gain, recurrent infections (URTI), and asthma. 2 years ago, headaches started after a traumatic brain injury, which aggravated her photosensitivity and audio sensitivity.

Medical history (including previous testing and treatments)

R.M. has been tested for multiple infections and she is Mycoplasma spp. Positive (+) (DNA test, blood & urine), Lyme positive (+) (Igenex Lab), Rocky Mountain Spotted Fever negative (-), Bartonella negative (-) Murine Typhus negative (-). Antibiotic treatment was attempted in 2012 but she was not able to tolerate the treatment back then for too long without significant side effects.

Adrenal 4-point cortisol test was done and was found to be on the lower end of the curve. MRI brain scan with contrast was performance with normal findings. She is also currently being treated with bio-identical hormones for menopause. No auto-immunity diagnoses.

The GAP (Genetic Assisted Prescribing) test was done, showing very good clearance of *phase 1* liver detoxification pathways for pharmaceuticals and toxicants (phase 2 not yet tested at this time).

Pre and post DMSA provocation was done in 2013 with her previous MD which found significantly high Post provocation lead levels when compared to other normal Provocation results (lead = 130ug/g Cr, normal non-concerning DMSA provocation levels should be around <20ug/g Cr). She did a series of IV chelation treatments which lowered her post provocation levels to 33ug/g Cr, resulting in only slight improvement in symptoms.

Assessment

After doing an initial environmental assessment for R.M. it was very clear that her past and present exposures may be playing a significant role in her symptoms. It was discovered that she had a fairly high total body burden of multiple exposures that correlated

very well with the onset of her symptoms, primarily solvents as a key exposure.

From the age of 18-35 she was a professional artist, working full time, specializing in fiber glass sculptures. During this time she was working indoors in a non-well ventilated warehouse with exposure to multiple chemicals such as melted styrofoam, rubber cement, dyes, acetone, solvents, and spray paints. During the winter, the poorly ventilated warehouses were heated with propane heaters. No protection was used during this time, and she reports being often covered past her elbows in acetone, varsol and other solvents.

Her exposure to solvents and other toxicants there was so high, especially during the winter, that she reported having 2 episodes of syncope on the subway on her way home. Her other exposures discovered were mold: growing up in an older home with dirt basement where she played there often. There was a recent flood in the apartment building where she lives at now (reports seeing some black mold afterwards in the building), but not in her unit.

Cigarette usage from age 15-35, sporadically. She also had a significant alcohol intake during most of her life, which she had to quit a few years ago. Fish intake was low throughout her life and mercury exposure was not a concern, as was seen in her pre & post provocation test results.

It was during this time (shortly after starting to work with solvents) that R.M. developed her symptoms, which matched very well to her environmental exposures. Short and long term exposure to solvents is known to cause fatigue, dizziness & balance issues, significant brain fog (poor concentration and focus, memory loss, difficulty reading, etc.), and weakened immune system that can lead to recurrent and chronic infections.[xv xvi]

Chronic Solvent Encephalopathy (CSE) is a well-known condition that is seen in people with long term exposure to solvents. At this point in the assessment, this was the primary working diagnosis. Tests were ordered to assess current exposures in her environment (to see if she has a current ongoing exposure to solvents), since she did report feeling better whenever she's away from home in the last few years. Genetic testing for phase 2 detoxification pathways were also completed.

Toxic Effects CORE Profile testing was completed by Genova Diagnostics: Blood Solvent panel came back high for current exposure of Styrene (0.22ng/mL (<0.12ng/mL) and some benzene (0.17 ng/mL). Blood levels for Chlorinated Pesticides and PCBs were low/not-detected. Organophosphate pesticides (urine metabolites) showed DMTP 50.88mcg/gm Cr (<30.48mcg/gm Cr), and low/non-detected levels in BPA, tricolosan, phthalates and parabens. See Table 1. The high solvent levels in her blood were later found to be potentially coming from her home environment. There were relatively high levels of VOCs detected in her apartment upon inspection, but the actual source was not identified.

Genetic testing (SNPs and CNVs) for detoxification, methylation and oxidative stress were also completed. See Table 2. The results clearly showed a significant reduction in her glutathione-s-transferase detoxification pathways, along with very poor methylation. The combination of these two findings reflects that her tolerance to daily toxicant exposure is hindered, let alone to the higher exposure she had earlier on in her life as reported above.

R.M. also filled out 3 validated questionnaires to help assess treatment outcome results. The Revised Fibromyalgia Impact Questionnaire (FIQR) - and the Fibromyalgia/Chronic Fatigue Syndrome Questionnaire – total score of 398 and the MSQ Detoxification Questionnaire. Please see Graph 1, 2 and 3.

Therapy and Outcome

Along with the specific environmental related treatments given below, R.M. was being treated by a team of professional practitioners for the following: lifestyle medicine (nutrition and lifestyle support), micronutrient supplementation for methylation support (active B-complex including 5-MTHF), omega3 fish oil (1320mg EPA/ 660mg DHA), probiotics, iron for anemia, and nebulized glutathione (2x/week). These were given to help support any suboptimal nutrient levels that may have been present, and the methylation deficiencies that were genetically found.

With regards to her environmental treatments, R.M. made sure her diet was completely organic to lower her current exposure to organophosphates. She had purchased a medical grade air filter (hyper-hepa filter with a high amount of activated carbon and potassium permanganate for VOC removal) and started taking nutrients for phase 1 and phase 2 detoxification pathway upregulation (especially solvent removal): Extra activated B6 and magnesium glycinate to bowel tolerance (both of which are essential co-factors for phase 1 detox pathways), N-Acetyl-Cysteine 500mg 2x/day (to help increase glutathione production), R+alpha lipoic acid, vitamin C 2000mg 2x/day (to help recycle glutathione and give extra antioxidant support). Taurine, glycine, and glutamine at 1000mg each 2x/day to help with phase 2 liver conjugation detoxification pathways for solvents (acylation pathway).

Activated charcoal was used (away from medications and natural products) to reduce enterohepatic recirculation of mycotoxins. Raw brassica family (broccoli, kale, arugula) smoothies daily were prescribed to enhance Glutathione-S-Transferase pathways (GST). Colon hydrotherapy treatments were also done when possible (1-2x/week), the purpose of which was again to reduce enterohepatic recirculation of toxins and toxicants. When done in a higher frequency of 2x/week, colon hydrotherapy treatments can sometimes trigger a bile release during the session that results in its rapid elimination before getting reabsorbed. This extra bile elimination is visible through the tube, usually at the end of the session, the water at this point is black, red, green, or yellow in appearance – and patients usually report feeling significantly better when this finally happens (this can take several sessions).

R.M. at first had difficulty with taking the full dosage of the above treatments, due to GI upset and nausea. After reducing the dosage, she was able to slowly increase them increase over the next few weeks without concern. During the next few months, R.M. reported feeling only a bit better (15-20%) with her usual on-going flare ups every few weeks. The improvement was significant for her compared to previous improvements, but still not what was hoped for at this time.

Her current living environment (being in the city, higher than normal VOC concentrations, potential and suspected mold at her apartment) was still suspected to be maintaining a high total body burden for her. It was at this point the R.M. decided to move out of the city to a much cleaner home environment in an attempt to improve her health.

Within weeks of moving out, R.M. reported significant overall improvement in her symptoms for the first time in years. After her move, she continued with the same protocol above and recently had attempted another trial of antibiotics for the above-mentioned infections. This time her tolerance to the treatment was greatly improved compared to her previous attempts in the past. It was very apparent that her previous apartment had been one of the primary ongoing exposures responsible for maintaining her symptoms.

After moving out, her score for the Revised Fibromyalgia Impact Questionnaire (FIQR) is 71 (reduced from 180) and the Fibromyalgia/Chronic Fatigue Syndrome Question-

naire score is 225 (reduced from 398). See Figure 1. There is still more improvement that is needed for her to achieve optimal health, but the significant improvement that was seen after moving away, while doing the treatment, from a potentially sick-building to a cleaner environment really highlights the necessity of reducing current total body burden and environmental exposures.

Table 1. Toxic Profile

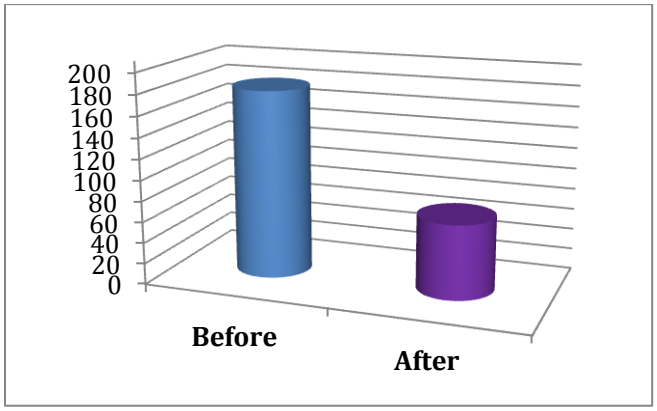
Styrene	0.22ng/mL	<0.12ng/mL (95th percentile)
Benzene	0.17ng/mL	<0.26ng/mL (95th percentile)
DMTP	50.8mcg/gm creatinine	<30.4mcg/gm creatinine (95th percentile)

Table 2. Genetic Profile

GSTT1 (Primary Glutathione biosynthesis)	Null/Absent
GSTP1	A/G
SOD2 (Superoxide Dismutase gene)	C/T
CYP1A2 (Phase 1 detoxification)	A/A
FUT2, MTHFR, SHMT1, MTRR (Methylation processes)	G/G, T/T, A/A, A/G

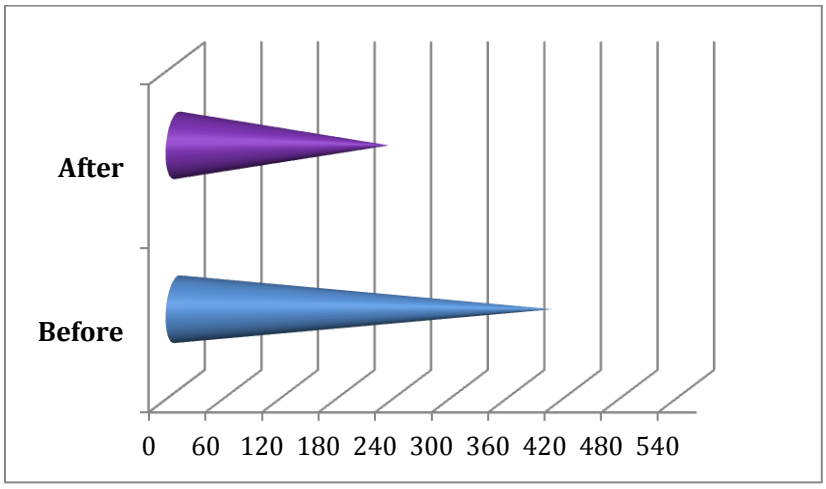
Graph 1: Revised Fibromyalgia Impact Questionnaire

Scale from 1 to 210; lower is better



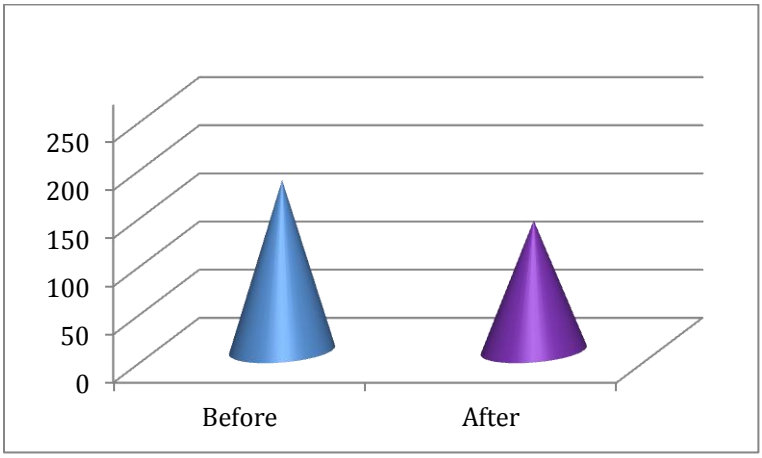
Graph 2: Fibromyalgia/ Chronic Fatigue Syndrome Questionnaire

Scale from 1 to 580; lower is better



Graph 3: MSQ Detoxification Questionnaire

Scale from 1 to 288; lower is better



Discussion

One of the biggest hurdles in complex patient cases that practitioners face, is not being aware of all the possible diagnosis that may explain the pattern of the symptoms patients present with. Nowhere is this more evident than in environmentally caused illnesses.

The reason for this is that Environmental Medicine is greatly missing from our education system. It is vital that doctors be able to recognize the symptom pattern of common daily exposures such as mold, solvents (VOCs), pesticides, heavy metals, phthalates, etc; especially when you consider the importance of individual genetic susceptibility to these.

In the case of difficult to treat conditions such as CFS, it is crucial that every doctor consider common everyday environmental exposures as a potential factor or even the primary cause for the condition. This can often result in near complete resolution of symptoms, or at the very least reduce one of the attributing factors that is adding to their overall symptom picture, resulting in significant quality of life improvements.

In the above cases both patients had clinically significant less fatigue, improved function as documented with both subjective and objective

outcome measures up to 12 months after treatment initiation. No serious adverse events arose over the course of treatment, suggesting that the patient responded well and all treatments were well tolerated.

This novel case study proposes that a functional medicine model emphasizing a thorough history and evaluation of current and past environmental exposures may be of benefit in the management of patients with chronic fatigue syndrome. Further investigations with larger homogenous patient populations in randomized blinded controlled trials would be warranted.

In this case report, instead of relying solely on the conventional diagnosis of CFS, the patient received an individualized functional medicine diagnoses with appropriate follow-up and treatments. In this case, the patient showed a positive response to personalized, multifactorial treatment and education on environmental hazards. Subjective outcome measures included the Medical Symptoms questionnaire, the Chronic Fatigue-Fibromyalgia Questionnaire and the Fibromyalgia Impact Questionnaire which all showed improvement from the time of diagnosis to the end of treatment.

It is important, especially in cases with CFS, to thoroughly evaluate the patient and search for potential environmental concerns or other underlying core problems that may affect mitochondrial function. The multifaceted decision-making process involves taking the time to educate on lifestyle and environmental factors that influence the disease process and intervening on multiple levels to restore function over time.

The functional medicine model is a personalized, system's biology approach that uses emerging research to address the fundamental mechanisms producing the symptoms. Although, many patients are given the same disease name, their stories are unique and the underlying dysfunctions and processes are specific to each patient.

The functional medicine approach seeks to understand how impairment in a system's upstream (cause) leads to pathology downstream, namely the disease or symptom (effect).

With the advent of the 'omics' revolution in the 21st century, it is timely to redirect medical care to a more personalized medical approach. By using a systems-oriented approach and engaging both patient and practitioner in a therapeutic partnership, functional medicine seeks to restore the patient's overall health. Functional medicine aims to address the whole person such that practitioners spend extended time with the patient, listening to the person's health history and then looking at the interactions among genetic, environmental, and lifestyle factors. As seen in this case study, the 'gene-environment' intersection is a core determinant of health and disease and epigenetics solutions can be applied for long-term, sustainable health and disease resolution.[xvii] In essence, the functional medicine model necessitates an evolution in the practice of medicine that would better address the health care needs of the 21st century.

This case study highlights the importance of patients' willingness to respond to changes in their environment, making the functional medicine model a good example of an individualized, patient care approach. While evidence-based medicine is critical in informing the treatment choices for isolated therapeutic agents, this approach constrains practitioner from employing a 'precision medicine' type of approach.[xviii]

Clinical research, which includes larger studies and specific patient cohorts compared to socio-economic costs, is needed to further validate such a model to improve overall patient care that might be provided to every patient.

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Lucia Romero, B.A. (Hons) is the Clinic Manager and Treatment Coordinator at the Centre for Advanced Medicine since 2012. Lucia has her Bachelor of Arts honours degree in Psychology with a minor in Law from Carleton University. She has appeared on local television broadcasts with Roger's Cable and is an advocate for Functional Medicine.

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