Refractory Depression, Fatigue, Irritable Bowel Syndrome, and Chronic Pain: A Functional Medicine Case Report

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ABSTRACT

Introduction: Single-disorder or single-organ-system clinical practice guidelines are often of limited usefulness in guiding effective management of patients with chronic multidimensional signs and symptoms. The presence of multiple long-standing medical problems in a given patient despite intensive medical effort suggests that addressing systemic core imbalances could complement more narrowly focused approaches.

Case Presentation: A 72-year-old man experiencing long-standing depression, fatigue, irritable bowel syndrome, and chronic pain in the context of additional refractory illnesses was assessed and treated, guided by a system-oriented approach to underlying core imbalances termed functional medicine. This patient was referred from a team of clinicians representing primary care, cardiology, gastroenterology, hematology, and psychology. Prior treatment had been unsuccessful in managing multiple chronic comorbidities. Diagnostic assessment included comprehensive stool and nutritional/metabolic laboratory testing.

Results: The blood-, urine-, or stool-based measurements of relevant markers for multiple systemic issues, including digestion/absorption, inflammation, oxidative stress, and methylation, identified previously unrecognized root causes of his constellation of symptoms. These functional measurements guided rational recommendations for dietary choices and supplementation. The patient experienced steady and significant improvement in his mental health, fatigue, chronic pain, and irritable bowel syndrome—as well as the unexpected resolution of his chronic idiopathic pancytopenia.

Conclusion: The success in this case suggests that other patients with chronic, complex, and treatment-refractory illness may benefit from a system-oriented assessment of core imbalances guided by specialized nutritional/metabolic and digestive laboratory testing.

INTRODUCTION

Single-disorder clinical practice guidelines are often of limited usefulness in guiding effective management of patients with chronic multidimensional signs and symptoms. The presence of multiple long-standing medical problems, despite excellent medical care, suggests that new questions or perspectives may be helpful. For example, assessment of underlying key common pathways for all diseases, such as gastrointestinal dysfunction, proinflammatory imbalance, and oxidative stress, could augment the more traditional organ-system-oriented, discipline-focused approach. The organizing principle of the approach taken here, termed functional medicine, is that restoration of health requires defining and addressing seven potential core imbalances that may underlie any given disease state. These seven categories are 1) assimilation (digestion, absorption, microbiomics, respiration), 2) defense and repair (immune function, inflammation, infection), 3) energy (production, regulation), 4) biotransformation and elimination (toxicity, detoxification), 5) transport (cardiovascular and lymphatic systems), 6) communication (hormones, neurotransmitters, cytokines), and 7) structural integrity (membranes, fascia, bacterial translocation). The core belief is that imbalance in one or more of these seven common disease pathways may be the root cause of many seemingly disparate conditions.

This case illustrates how specialized laboratory testing identified previously unrecognized physiologic and biochemical dysfunction in a complex patient. This dysfunction in several common disease pathways was both clinically relevant and inexpensively modifiable. The result was substantial clinical improvement and a markedly improved patient quality of life.

CASE PRESENTATION

Initial Visit (February 2012)

A 72-year-old man was referred to a board-certified internist specializing in complex, refractory illnesses in February 2012. The patient's primary goal, stated at his first visit, was to "walk

Table 1. Medical history timeline

1940s	Heartburn and gastric reflux
1950s	Depression since adolescence
1960s	Began smoking; increased alcohol consumption
1999	Pancreatitis, alcoholic hepatitis, and liver failure (subsequently resolved)
2004	Idiopathic pancytopenia; no alcohol consumption beginning in 2004
2012	Type 2 diabetes mellitus
2012	Specialized digestive and nutritional laboratory testing
2012-2015	Treatment for pancreatic insufficiency, nutritional and digestive imbalances
2013	Resolution of idiopathic pancytopenia and irritable bowel syndrome; decreased depression, fatigue, and pain

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out of the office with more hope." He wrote that it was "very hard to function. I wake after 9 hours of sleep and still feel tired. I don't have the emotional or physical strength to accomplish much. This is frustrating and I am on a cycle of becoming more depressed, more frustrated, and more helpless."

In addition to chronic fatigue and depression, the patient reported 1) heartburn, frequent gas, bloating, and diarrhea alternating with constipation; 2) right lower quadrant abdominal cramping, worsening after bowel movements; and 3) widespread arthralgias and myalgias. See Table 1 through 6 (Tables 4 and 5 available online at: www.thepermanentejournal.org/files/15-242.pdf), and the Sidebar: Important Medical History for a list of the patient's medical considerations.

Initial Clinical Findings

Patient-reported outcome instruments (higher scores indicate worse symptoms):

- Brief Fatigue Inventory: total fatigue interference score of 37/60
- Brief Pain Inventory: total pain interference score 36/70
- Patient Health Questionnaire-9: total score 13 (moderate depression 10-14).

Physical Examination

- Blood pressure 118/54 mmHg, pulse 74 beat/min and regular. Body mass index, 21.6 (calculated as weight in kilograms divided by height in meters squared)
- Anicteric with clear lungs and normal cardiac examination
- Abdomen tender to palpation of the right upper quadrant and epigastric area
- No hepatosplenomegaly
- Palpation in the left lower quadrant resulted in right lower quadrant discomfort
- No ascites present
- No edema in extremities (cool, pale fingers with slow capillary refill)
- No palmar erythema
- No asterixis.

DIAGNOSTIC ASSESSMENTS

The patient's concern of a reduced quality of life secondary to depression, fatigue, and gastrointestinal distress was part of a remarkable medical history as a survivor of end-stage liver failure and alcoholism. However, his depression, fatigue, widespread pain, and gastrointestinal symptoms did not resolve from medical treatments of specific diagnoses and individual symptoms. A clinical decision was made to evaluate the root causes of this patient's symptoms from a functional medicine perspective with comprehensive and structured stool[1,2] and nutritional diagnostic panels. A Comprehensive Digestive Stool Analysis 2.0 (CDSA 2.0) and Nutritional Evaluation (NutrEval) from a Clinical Laboratory Improvement Amendments-certified laboratory (Genova Diagnostics, Asheville, NC) were ordered. These kits offer bundled laboratory tests that provide insight into the function and status of several of the core pathways. Additionally, given the presence of environmental stressors and a decreased sense of personal efficacy, he was referred for Resilience Training or Mindfulness-Based Stress Reduction.

OTHER RELEVANT LABORATORY RESULTS

This patient had previously been found to be vitamin D deficient. However, he was not on vitamin D supplementation at his first visit and supplementation (2000 IU) was begun. In addition this patient's dehydroepiandrosterone-sulfate (DHEAS) level was low normal and DHEA 5 mg sublingually each morning was started.[3]

FOLLOW-UP AND OUTCOMES

The patient was evaluated four times between April 2012 and January 2013. With each subsequent visit, he reported steady improvement in his mood, overall energy, and chronic pain. He was compliant with the dietary recommendations and supplements outlined in Table 3. He elected to not pursue Resilience Training or Mindfulness-Based Stress Reduction.

He experienced minor episodes of dizziness with two near syncopal episodes, for which he was referred to his cardiologist.

Table 2. Medications and supplements at presentation

Medications	Dosage
Lisinopril/hydrochlorothiazide	40 mg/25 mg/d
Trazadone	150 mg/d
Effexor	225 mg/d
Ranitidine	75 mg 2x/d
Cilostazol	1 tablet 2x/d before meals
Atorvastatin	10 mg/d
Cytomel	5 μg/d
Nonsteroidal anti-inflammatory drugs	As needed
Rolaids	As needed
Supplements	
Centrum silver multivitamins	1 tablet/d
Folic acid	400 μg/d
Glucosamine/chondroitin	1500 mg/1200 mg 2x/d
Vitamin B6 (pyridoxine HCL)	50 mg/d

Important Medical History

1. Gastric reflux since childhood
2. Depression since adolescence with persistently elevated Patient Health Questionnaire-9 scores as an adult, consistent with moderately severe depression
3. Twenty pack-year smoking history (quit smoking March 1996)
4. Alcoholism (age 28 to 62 years): alcoholic hepatitis, chronic pancreatitis, pancreatic pseudocyst, and liver failure in 1999—successfully sober since 2004
5. Successful discharge from hospice with resolution of end-stage liver failure, 2004
6. Cardiovascular disease: hypertension, dyslipidemia, coronary stents, and claudication
7. Diagnosed with idiopathic pancytopenia in 2004
8. Type 2 diabetes mellitus since 2012
9. Osteoarthritis
10. Homocysteinemia with homozygous MTHFR (methylenetetrahydrofolate reductase C677T) polymorphism
11. Surgical history: cholecystectomy, tonsillectomy, and anal fissure repair

Repeat testing at his local hospital in December 2012 demonstrated persistent pancreatic insufficiency with an undetectable pancreatic elastase 1 and persistent *Candida glabrata* overgrowth in the stool even though the patient was no longer symptomatic. These findings supported continued prescription of pancreatic enzyme support, probiotics, and a diet rich in prebiotics. The patient's oncologist noted an "inexplicable resolution" of the patient's idiopathic pancytopenia in July 2013 and reported that his physical and laboratory examinations were normal at that time.

In January 2013, patient-reported outcomes had improved significantly:

- Brief Fatigue Inventory: total fatigue interference score of 19/60
- Brief Pain Inventory: total pain interference score 20/70
- Patient Health Questionnaire-9: total score 10.

DISCUSSION

Mental health disorders and gastrointestinal complaints are often components of complex, chronic illnesses that can challenge linear pharmacologic management.[4,5] System-oriented, functional

Table 3. Stool and urine metabolic testing results and therapeutic interventions

Visit no.	Laboratory biomarkers[a]	Diagnostic significance	Therapeutic interventions
1	Pancreatic elastase-1 < 15 (Ref: > 201 μg/g) Fecal fat 50.1 (Ref: 2.6-32.4 mg/g) Long chain fatty acids 43.8 (Ref: 1.3-23.7 mg/g) Phenylacetic acid (PAA) 0.32 mmol/mol creatinine (Ref: ≤ 0.12)	Pancreatic exocrine insufficiency	Pancrelipase 12,000 units with each meal
2	*Candida glabrata* 2+ (Ref: potential pathogen) Arabinose 158 (Ref: ≤ 96) Tartaric acid 66 (≤ 15)	Yeast overgrowth (sensitive to fluconazole)	Fluconazole 100 mg daily for 4 weeks
3	No growth for beneficial bacteria (*Lactobacillus*, *E coli*) 4+ growth (*Citrobacter braakii* and *youngae*) Dihydroxyphenylpropionic acid 6.1 (Ref: ≤ 5.3) Benzoic acid 0.06 (Ref: ≤ 0.05) Hippuric acid 611 (Ref: ≤ 603)	Dysbiosis	Probiotics (multiple: *Lactobacillus* and *Bifidobacteria* species plus *Saccharamyces boulardii*) daily Soluble/insoluble fiber-containing foods in diet
4	Methylenetetrahydrofolate reductase polymorphism Sarcosine 53 (Ref: ≤ 48)	Impaired folate cycle and methylation pathways	Discontinue folic acid supplementation Switch to L-5-methyltetrahydrofolate 400 μg/d plus vitamin B12 as methylfolate 500 μg/d
5	Lysine 39 (Ref: 45-286) α-Aminoadipic acid < detection limit (Ref: 11-73) Glycine 341 (Ref: 639-3306) Histadine 242 (Ref: 271-993)	Insufficient amino acids	Lysine 1000 mg/day for 2 months Glycine 1000 mg/day for 2 months Chew proteins thoroughly (eat slowly)
6	Cystathionine 4 (Ref: 6-33) Glutathione 486 (Ref: ≥ 669 μmol/L)	Impaired trans-sulfuration pathways	Pyridoxal-5-phosphate (vitamin B6) 50 mg/d Molybdenum 75 μg/d (multivitamin)
7	Ethanolamine 71 (Ref: 208-514) Glycine 341 (Ref: 639-3306)	Impaired choline metabolism	Eat lecithin-containing foods (eg, egg yolks, peanuts) Support folate cycle and methylation
8	Adipic acid 3.9 (Ref: ≤ 2.8) Borderline elevated beta-OH-butyric acid 2.0 (Ref: ≤ 2.8) Borderline elevated HMG 12 (Ref: ≤ 15) Borderline elevated ornithine 20 (Ref: 4-21)	Impaired energy production, ketosis Beta-oxidation of fats Pyruvate dehydrogenase (carbohydrate metabolism) Oxidative phosphorylation	Add magnesium glycinate 400 mg/d B vitamin support (multivitamin) Alpha-lipoic acid 200 mg/d Liberalize carbohydrate intake Eat more frequently
9	8-OH-dG 18 (Ref: ≤ 15 μg/g creatinine) Cysteine 82 (Ref: 21-78) Glutathione 486 (Ref: ≥ 669 μmol/L) Pyroglutamic acid 48 (Ref: 16-34) Coenzyme Q10 0.20 (Ref: 0.43-1.49 μg/ml)	Excessive oxidative stress/ overwhelmed defense mechanisms	Coenzyme Q10 (Ubiquinol) 200 mg/d Alpha-lipoic acid 200 mg/d Support glutathione production via transsulfuration Support glutathione production via diet: foods rich in vitamins E and C and sulfur Avoid use of acetaminophen
10	Omega 3 index 3.0 (Ref: ≥ 4.0) Vaccenic acid 1.18 (Ref: ≤ 1.13 wt %) Eicosapentaenoic acid 0.29 (Ref: ≤ 0.26 wt %) Arachidonic acid 22 (Ref: 15-21 wt %)	Long-chain omega-3 fatty acid insufficiency with omega 6 excess	Omega-3 fatty acid: 2 g EPA and DHA/d Cook with olive oil (low heat) or high-oleic acid safflower oil (higher heat)

[a] All biomarkers reported in μmol/L creatinine unless otherwise noted.
DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HMG = hydroxymethylglutaryl; Ref = reference; wt % = weighted percentage.

Table 6. Patient-reported outcome instrument scores[a]		
Instruments	**February 2012**	**January 2013**
Brief Fatigue Inventory	37	19
Brief Pain Inventory	36	20
Patient Health Questionnaire-9	13	10

[a] Higher score equals worse symptoms.

medicine approaches, supported by laboratory findings, can help engage patient and clinician in a therapeutic partnership to address genetic, environmental, and lifestyle factors that may be important in complex, chronic diseases.[6]

The intersection of depression, fatigue, widespread pain, and gastrointestinal symptoms in this patient had implications in multiple systems.[7,8] This justified a switch in the diagnostic focus from the customary organ-based systems to whole-body systems. Table 3 delineates the systemic issues important in this case, such as inflammation, oxidative stress, or impaired methylation. The blood-, urine-, or stool-based measurements of the relevant markers for each issue guided rational recommendations for dietary choices and supplementation.

Addressing systemic issues in chronic, complex illness complements a more traditional organ-system approach. In this case, addressing one fundamental imbalance may have addressed several disparate conditions. For example, diagnosing and addressing this patient's digestive dysfunction and the intestinal ecology imbalances not only improved digestive function but also improved several metabolic and nutritional markers known to be correlated with depression, fatigue, and myalgias.

Likewise, the reduction in his myalgias allowed this patient with diabetes with proven atherosclerosis to remain on atorvastatin. HMG Co-A reductase inhibitors (statins) are known to block production of coenzyme Q10; however, supplementation is not routinely recommended. The very low serum coenzyme Q10 measured in this patient suggested that supplementation might be of benefit.[8,9] The reduction in his arthralgias also allowed this patient who presented with low glutathione levels to avoid acetaminophen (which depletes glutathione). His low levels of glutathione were treated with a diet rich in vitamins C, E, molybdenum, selenium, and methionine- or cysteine-containing amino acids. The improved levels of both coenzyme Q10 and glutathione enhanced native oxidative stress management, known to help reduce pain, depression, and fatigue.[10] Finally, correction of all these systemic issues may have contributed to the unexpected resolution of his idiopathic pancytopenia after eight years.

CONCLUSION

David Sackett, one of the pioneers of evidence-based medicine, said "Without clinical expertise, even excellent evidence may be inappropriate for an individual patient."[11] The comprehensive approach outlined here integrated the clinical expertise found in organ-system-based disciplines with the perspective of functional medicine's systems-biology approach. This integration was possible because of external evidence from specialized stool and nutritional diagnostic panels. This combination resulted in effective management of multiple comorbidities that had previously been minimally responsive to treatment. The interference score for this patient's chronic fatigue was reduced by nearly 50% (from 37/60 to 19/60). The interference score for his chronic pain was reduced by nearly 40% (from 36/70 to 20/70). His Patient Health Questionnaire-9 score declined by 25% (13 to 10). His gastrointestinal function improved greatly without significant increases in pharmaceuticals. Therapeutic recommendations were based on measurements of nutritional and digestive status and function. The success in this case suggests that other patients with chronic, complex, and treatment-refractory illness may benefit from a functional medicine, system-oriented approach guided by nutritional and digestive laboratory testing.

Patient Perspective

"I experienced at least a 50% reduction in pain and improvement in my quality of life. My anxiety is reduced, I am more relaxed, and feel stronger. The most helpful has been the work with my gut issues. I am almost like clockwork now." ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose. Written consent was obtained from the patient for publication of this case report.

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