

Major Depressive Disorder and Food Hypersensitivity: A Case Report

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Keywords

Depression · Mental health · Nutrition · Diet · Food sensitivity · Hypersensitivity · Gluten · Gluten-free diet · Dairy-free diet

Abstract

Introduction: Major depressive disorder (MDD) is a common chronic mental health condition and not all patients respond to pharmacotherapy. Increasing evidence suggests that dietary choices play a role in the pathogenesis of mental illness and serve as modifiable factors with utility in the treatment of these disorders. Although many mechanisms are being explored, one area of study is the role of food hypersensitivity reactions in mental health conditions. **Case Presentation:** This article reports on a 34-year-old female patient with MDD whose symptoms improved in response to a dietary intervention involving the elimination of common food allergens. Reintroduction of the foods on several occasions was associated with a worsening of mood symptoms. Serum IgG testing reported results consistent with the reintroduction challenge. **Discussion and Conclusions:** Hypothesized mechanisms underlying the potential relationship between food hypersensitivity and MDD are presented. Further research in this area is warranted.

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Introduction

Major depressive disorder (MDD) is a common, serious, and recurrent disorder with a significant impact on quality of life, wellbeing, and productivity along with a substantial health care cost [1]. In Canada, MDD is the second leading cause of disability adjusted life years [2] and is the primary cause of poor health and disability worldwide, with 300 million people diagnosed with depression [3].

MDD is typically treated with pharmacotherapy, psychotherapy, or a combination of these approaches [4]. It is estimated that a partial response to medications is observed in half of primary care patients presenting with depression. Of those patients who are treated with a single antidepressant, one-third achieves remission. The STAR*D study tested sequential pharmacological treatments and demonstrated remission rates of approximately 18–30% with each intervention and lower response rates after several successive trials [5].

The evidence to support nutritional psychiatry is building and includes robust observational data and new intervention data [6]. A recent meta-analysis found that a healthy diet pattern including more vegetables, fruit, and whole grains is associated with a 30% reduction in the risk of depression while increased consumption of pro-

cessed food was associated with an increased risk of depression [7]. Recently, a randomized controlled trial explored the efficacy of adjunctive dietary counseling using a modified Mediterranean diet. The intervention group achieved a significantly greater reduction in depression symptoms as well as significantly higher rates of remission compared to the social support control groups (NNT 4.1, 95% CI 2.3–27.8) [8].

The term “food hypersensitivity” describes adverse reactions to food such as food intolerances and food allergies, which are immune responses mounted after the consumption of various foods or food additives [9]. Approximately 90% of food allergies are related to 8 types of food: milk, eggs, peanuts, tree nuts, fish, shellfish, soy, and wheat [10]. Reactions can range from mild to life threatening [11].

Food allergies occur as a result of IgE-mediated reactions involving mast cell activation and histamine degranulation [12]. In contrast to food allergies, food intolerances include a range of adverse reactions to a particular food or food additive that may or may not be characterized by immune system involvement [13]. For example, deficiencies in the digestive enzyme lactase result in lactose intolerance. Food intolerances are common in the developed world, affecting 15–20% of the population [9]. Symptoms may include nausea, bloating, abdominal pain, or diarrhea, occurring 30 min to 48 h after ingestion of the offending food or drink. While digestive symptoms are most common, extraintestinal symptoms including migraines, malaise, asthma, and eczema have also been associated with adverse food reactions [9]. The diagnosis of food intolerance is typically established using elimination and challenge testing of suspected foods [13].

Alternately, food sensitivity testing involves the *in vitro* exposure of a patient’s blood sample to various foods or food constituents to ascertain the extent of IgG antibody binding, as part of the immunologic response to the food antigen. A wide range of foods are tested, and the quantification of IgG binding to each food is completed via enzyme or fluorescence-linked immunosorbent assays. Many conditions exhibit a potential correlation with the deposition of allergen IgG complexes including weight gain, asthma, inflammatory bowel disease, irritable bowel syndrome (IBS), and depression [14]. The validity of the IgG food sensitivity test has been questioned over the years [15]. Recent studies, however, have shown that the IgG food reaction may provide clinically meaningful results in a wide variety of conditions. One study of 114 patients with a history of IgG food sensitivity demonstrated that 71% of symptoms improved by 75% or more after

elimination of positive foods, including asthma, headaches, coughing, skin rash, bloating, and diarrhea, among others [16]. A hypoallergenic/elimination diet has also demonstrated clinical benefit in gastrointestinal conditions such as IBS [17, 18] and inflammatory bowel disease [15]. Drisko et al. [18] observed a marked improvement in patients with IBS who eliminated foods eliciting raised serum IgG antibodies compared to those who did not. IgG food sensitivity testing may also be clinically relevant in mental health conditions including autism [19] and bipolar disorder [20]. A correlation has been found between anti-casein IgG antibodies and a diagnosis of bipolar I, potentially implicating a role of immune activation as a result of casein exposure as a part of the conditions’ pathogenesis [20]. Furthermore, participants with autistic disorder exhibited significantly increased plasma concentrations of IgG antibodies against casein [19].

The possible connection between food hypersensitivity reactions and mental health is an expanding area of research. A 2013 meta-analysis demonstrated elevations of 5 biomarkers characteristic of gluten sensitivity in non-affective psychosis populations [21].

There is also a body of evidence potentially linking celiac disease (CD), which involves an immune reaction to gluten and consequent intestinal inflammation and damage, with compromised mood health [22]. In one study population, it was shown that one-third of celiac patients were affected by depression, compared to one-tenth of chronic hepatitis patients [23]. A large prospective study of patients with CD found an 80% increase in the risk of a subsequent depression diagnosis [24]. Psychological distress in 21 recently diagnosed CD patients was significantly reduced after the initiation of a gluten-free diet [25]. Case reports of CD patients whose depression failed to respond to pharmacotherapy but remitted with a gluten-free diet have also been documented [26, 27]. Furthermore, a number of intervention studies have explored the utility of the gluten-free diet in autism spectrum disorders with promising results in development and autistic traits [28, 29]. A gluten-free diet has also shown benefit in patients with schizophrenia in a small open label study [30]. A double-blind crossover study assessed the impact of gluten ingestion on mood in non-CD patients. Dietary challenges of gluten or placebo were administered in 22 IBS patients whose symptoms were previously controlled with a gluten-free diet. Higher state depression scores were correlated with gluten ingestion [31].

Despite this body of observational evidence and small number of intervention studies suggesting a possible connection between improved mood with gluten avoidance,

Table 1. Food to include and avoid during the elimination phase

Category	Include	Avoid
Vegetables	All others	Tomatoes, potatoes, peppers, eggplant, corn
Fruit	All	
Grains	Brown rice, quinoa, buckwheat, millet, tapioca, amaranth	Wheat, spelt, rye, oats, barley, kamut
Legumes	Beans, lentils, peas	Soy
Animal products (meat, dairy, eggs)	Chicken, Turkey, lamb, wild game, fish	Processed meat (cold-cuts, hot dogs), red meat, shellfish, dairy, eggs
Nuts and seeds	All other nuts and seeds	Peanuts
Condiments	All herbs and spices Stevia	Margarine and shortening All sweeteners (syrups, honey, brown/white sugar)
Beverages	Water, herbal teas, green tea, 100% fruit or vegetable juice, rice/almond milk	Coffee and black tea, alcohol, soda pop

there is a lack of research in a clinical psychiatric population. Many of the studies measured depression symptoms in participants with CD or nonceliac gluten sensitivity but not patients with diagnosed psychiatric illness. Two previous case reports were identified that described improvement of severe [32] and treatment-resistant [33] depression, which resolved with elimination of specific foods. This case report details the use of an elimination diet in another patient with MDD.

Case Presentation

Presenting Concern

JK is a 34-year-old Caucasian woman employed as a social worker. She presented with concerns of MDD, generalized anxiety disorder, weight management, and constipation.

She had previously used pharmacotherapy in the treatment of her mood and anxiety disorders but had chosen to discontinue treatment 5 years ago due to unwanted side-effects. She was interested in nonpharmacologic interventions including dietary approaches.

JK met the DSM criteria for MDD including periods of low mood and indifference, difficulty sleeping, increased appetite, loss of pleasure, and fatigue.

JK's depression started at 12 years of age but was not treated until 20 years of age. She was prescribed venlafaxine but did not find it very helpful. Additionally, she experienced side effects such as headaches and vomiting at higher doses of the medication. She also participated in counseling and used an app-based cognitive behavioral therapy tool, which she found moderately helpful.

Clinical Findings

A diet history was obtained through a 24-h Diet Recall [34]. It revealed the following food intake at the baseline appointment:

Breakfast: none

Lunch: hamburger and French fries

Dinner: pizza from the grocery store

Snacks: popcorn, chips

She reported frequently eating other convenience food items such as submarine sandwiches, pre-made food from the grocery store, donuts, and cookies.

Physical activity: The patient was not engaging in physical activity.

Past Medical History and Psychosocial History

JK previously suffered from a substance use disorder from ages 19 to 22 with a high intake of alcohol. She experienced constipation with an average of 1–2 bowel movements per week with stool being difficult to pass and concurrent bloating. She also reported cold hands and feet in addition to easy bruising. She described initiation insomnia with an average of 2 h needed to fall asleep. Last, she experienced acne vulgaris on her face that began in adulthood. JK has a history of early life trauma including an alcoholic parent.

Diagnostic Focus and Assessment

Screening physical examination was unremarkable apart from mild facial acne. JK is 5'5 tall and weighs 175lb (BMI = 29.1).

Therapeutic Focus and Assessment

JK was prescribed a hypoallergenic diet for 3 weeks (the "elimination phase"). Following the elimination phase, she was instructed to reintroduce one food every 3 days by consuming it twice per day while observing for any reactions (the "reintroduction phase"). Table 1 for a list of foods included and excluded on this diet.

Follow-Up and Outcomes

At the first follow-up appointment 2 weeks later, JK reported that she complied with the prescribed diet for the entire 2-week period – this was assessed by querying the patient about consumption of food that she was instructed to avoid. Using a 24-h recall, she reported a food intake as follows:

Breakfast: smoothie made of fruit, water, ice, and protein powder

Lunch: salad with chicken

Dinner: chicken and brown rice pasta with vegetables

Snacks: fruit and almonds

During the elimination phase, she noticed improved mood with fewer days of low mood, less episodes of crying, and an increase in interest in activities. Additionally, she reported increased energy, mental clarity, and frequency of bowel movements (once every 2 or 3 days). She also reported a 10 lb weight loss and a resolution of the acne lesions.

Another follow-up visit was completed 3 weeks later, JK reported that during the reintroduction phase, the consumption of dairy products resulted in a rapid onset (<24 h) of low mood symptoms including feelings of sadness and increased crying. Additionally, gluten and dairy reintroduction were associated with headaches, gas, bloating, and abdominal discomfort. She did not attribute these changes in mood to any other concurrent changes in her lifestyle or events in her life.

Following the use of the elimination diet, additional therapies were prescribed including fish oil supplementation (1,300 mg Eicosapentaenoic acid, 200 mg Docosahexaenoic acid, 6.7 mg vitamin E per day), intramuscular vitamin B12 injections (1,000 mcg), and exercise. She reported that these recommendations were associated with an improvement in mood regardless of diet; however, while utilizing these strategies, changes in diet still affected her mood.

Over the following 2 years, the patient returned to the clinic approximately every 3 weeks. She had difficulty maintaining the diet changes and returned to her previous dietary patterns 5 times before restarting the elimination diet again. Each time she resumed the elimination diet, by avoiding foods she had previously identified as reactive, she noticed an improvement in her mood and constipation. Reverting to her previous diet resulted in a worsening of her mood and constipation as well as headaches. Follow-up clinical encounters included motivational interviewing to assist JK in returning to her prescribed diet.

Subsequently, the patient completed IgG testing at a single time point and the report identified wheat, casein (a protein found in dairy products), and yeast as being highly reactive. These results provided further motivation for the patient to continue complying with the diet changes that have helped in managing her symptoms.

Discussion

This case report details the treatment of a 34-year-old woman with MDD who experienced relief of depression symptoms while following a prescribed hypoallergenic diet as well as worsening of symptoms with reintroduction of certain foods. Serum IgG testing results were consistent with the reintroduction challenge.

One strength of this case is that the hypoallergenic diet was the only intervention prescribed at the time when JK reported improvement and subsequent worsening of her symptoms with reintroduction of the reactive foods. Additionally, the consistent findings between the diet and IgG testing add strength. A limitation of this case is that validated assessment tools were not employed to monitor the change in JK's mood disorder severity – only the patient's subjective assessment of symptom severity was provided; however, significant improvements in core depression symptoms such as low mood and interest were noted. Diet at baseline and follow-up was assessed using the 24 h diet recall, and adherence to the therapeutic diet was assessed by querying the patient about consumption of the avoided foods. No assessment of the quantity of food was made as the primary goal of the intervention was to modify the types of food eaten and not the amount. This was because the patient's other symptoms (headaches, constipation, bloating) led the clinician to hypothesize that JK was experiencing an adverse food reaction.

Several mechanisms have been proposed to explain a possible role of food sensitivities in mental health. There is a known connection between the nervous and digestive systems, often termed the “gut-brain axis.” Various neurotransmitter and neuropeptides mediate signaling between these 2 systems [35], with 90% of the body's serotonin being synthesized in the gut [36]. The gut microbiome is hypothesized to play a significant role in affecting mood, behavior, and inflammation through a relationship that is bidirectional [37–39].

One mechanism that has received significant attention is inflammation. There is a growing body of evidence that supports a role of inflammation in the pathogenesis of mental illness [40, 41]. Patients with depression have higher levels of inflammatory cytokines in systemic circulation and cerebrospinal fluid. Inflammation decreases dopamine production, increases enzymatic degradation of tryptophan and serotonin, as well as monoamine reuptake. In the presence of inflammation, the enzyme indole 2,3 dioxygenase converts tryptophan, the precursor of serotonin, to kynurenine thereby decreasing serotonin levels [37]. Patients with higher levels of inflammation are less responsive to psychopharmacology [42]. Studies employing anti-inflammatory agents to treat inflammatory conditions demonstrate an improvement in depressive symptoms prior to an amelioration of the underlying condition [43] and although not all intervention studies are consistent, a recent meta-analysis of studies employing medications with anti-inflammatory effects found

improved depression symptoms and increased rates of remission [44].

Inflammation may also mediate food sensitivities by increasing intestinal permeability, a process that involves compromise of the intestinal epithelial barrier function and allows for the absorption of intestinal antigens. These foreign molecules lead to the development of an IgG mediated immune response. As a result, an inflammatory response occurs, sustained by chronic exposure to the dietary antigen [37].

Another hypothesis that has been proposed is a direct psychoactive action of food constituents or their derivatives. One of the proteins found in cow's milk, beta caseomorphin-7, has received attention for its ability to stimulate opioid receptors and trigger the release of histamine [45].

There are many other hypothesized mechanisms for how dietary modification may have an impact on mental health beyond the adverse effects of food allergens. Certain constituents such as omega-3 fatty acids and folic acid have documented antidepressant actions [6]. In addition to eliminating food allergens, JK significantly improved the overall quality of her diet by reducing the consumption of processed food and including more nutrient-rich unprocessed foods as well as decreasing many "proinflammatory" foods and increasing "anti-inflammatory" ones. It is possible that changes in levels of micro or macronutrients may have been responsible or partially responsible for the symptomatic improvement; however, the timing of the worsening of symptoms is not consistent. JK reported an onset of low mood within 24 h of consuming dairy, which is more consistent with the time of response of an adverse food reaction [9].

Metabolic factors related to weight may play a role in depression. Obesity and depression are highly cooccurring, and the treatment of either condition is associated with improvement of the other [46]. This patient reported a 10-pound reduction in weight during the elimination phase of the diet, which may have impacted her mental health. Another possible explanation for JK's clinical improvement is the placebo effect. A blind, placebo-controlled study that employed a diet intervention in patients with rheumatoid arthritis involving the avoidance of food intolerances and found a significant benefit. They noted that, while not as large as the intervention group, the placebo group did experience a benefit [47].

While it is well known that diet choices have a significant impact on health, modifying diet behavior and maintaining changes are difficult [48]. In this case, JK was very open to dietary modification. She was dissatisfied with

the depression treatments that she had tried previously and was willing to try any intervention that might be helpful, including something as challenging to implement as major dietary changes. Also, in the course of the clinical assessment, she expressed awareness of the poor quality of her diet and openness to dietary modification as an intervention. This case demonstrates the difficulty of maintaining lifestyle changes as the patient relapse to her prior diet several times. Motivational interviewing techniques were used at follow-up appointments to assist the patient in returning to her improved diet habits. Other research on patient adherence to therapeutic diets, although in a different patient population, reported barriers such as motivation, time, perceived benefit, lack of social support, cultural patterns of food consumption and facilitators such as social support, relationship with healthcare providers, and use of intervention such as motivational interviewing [48]. JK reported that remembering how she felt during the elimination phase inspired her to return to the diet after she had set backs so perceived benefit of the diet appeared to be a significant motivator in this case.

Conclusion and Further Research

Food hypersensitivity reactions may play a role in the development or progression of mood disorders and the systematic identification of food triggers using an elimination/reintroduction diet may be a valuable tool in assessing and treating mood disorders. This case adds to a body of preliminary literature suggesting that further research is warranted. This could be in the form of randomized trials comparing mood effects of the elimination/reintroduction diet to a control diet. Alternately, patients who complete an elimination/reintroduction diet could be exposed to blinded reintroductions of reactive foods while monitoring changes in mood symptoms. These studies could further elucidate the potential usefulness of identifying and avoiding food sensitivities in patients with MDD.

Disclosure Statement

The authors declare no conflicts of interest.

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