Relief of Fibromyalgia Symptoms Following Discontinuation of Dietary Excitotoxins

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BACKGROUND: Fibromyalgia is a common rheumatologic disorder that is often difficult to treat effectively.

CASE SUMMARY: Four patients diagnosed with fibromyalgia syndrome for two to 17 years are described. All had undergone multiple treatment modalities with limited success. All had complete, or nearly complete, resolution of their symptoms within months after eliminating monosodium glutamate (MSG) or MSG plus aspartame from their diet. All patients were women with multiple comorbidities prior to elimination of MSG. All have had recurrence of symptoms whenever MSG is ingested.

DISCUSSION: Excitotoxins are molecules, such as MSG and aspartate, that act as excitatory neurotransmitters, and can lead to neurotoxicity when used in excess. We propose that these four patients may represent a subset of fibromyalgia syndrome that is induced or exacerbated by excitotoxins or, alternatively, may comprise an excitotoxin syndrome that is similar to fibromyalgia. We suggest that identification of similar patients and research with larger numbers of patients must be performed before definitive conclusions can be made.

CONCLUSIONS: The elimination of MSG and other excitotoxins from the diets of patients with fibromyalgia offers a benign treatment option that has the potential for dramatic results in a subset of patients.

KEY WORDS: aspartame, fibromyalgia, monosodium glutamate.

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Fibromyalgia syndrome occurs in 3–6 million patients in the US.[1] It is the third most commonly diagnosed rheumatologic disorder (after osteoarthritis and rheumatoid arthritis). Most patients are women, with a median age of onset of 29–37 years; the median age of formal diagnosis is 34–53 years.[2]

This disabling disorder is characterized by widespread pain and tenderness, fatigue, morning stiffness, and sleep disturbance (Table 1).[1,3] Diagnosis criteria have been developed by the American College of Rheumatology (Appendix I),[3] but, unfortunately, the cause of fibromyalgia syndrome is unknown. Theories have included alterations in neurotransmitter regulation (especially serotonin); hormonal control problems (especially of the hypothalamic–pituitary–adrenal and growth hormone axes); immune system dysfunction; problems in sleep physiology; abnormal perception of bodily sensations; stress; viral pathologies; local hypoxia; and disturbances in muscle microcirculation, adenosine monophosphate, and creatine concentrations.[1] Current evidence[4-6] most strongly supports a neurochemical or neurohormonal hypothesis.

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We describe four patients who experienced a dramatic recovery from fibromyalgia syndrome by eliminating certain preservatives and food additives, mainly monosodium glutamate (MSG), from their diet. All four patients had fibromyalgia syndrome characterized by tenderness and pain at all tender points, fatigue, sleep disorders, and irritable bowel syndrome (Table 1). This appears to be the first such report in the medical literature, based on the absence of results in a MEDLINE search.

CASE REPORTS

CASE 1

A 40-year-old white woman was diagnosed in 1987 with moderately aggressive fibromyalgia symptoms that had been very difficult to manage with traditional approaches. She also had atypical chest pain and carpal tunnel syndrome. This patient did a tremendous amount of reading in the lay press regarding fibromyalgia, allergies, food allergies, and "food toxins." She treated her daughter, who had a number of skin allergies, with a diet that was basically additive-free, with an emphasis on corn derivatives and MSG. When her daughter's allergy problem resolved, the woman decided to follow the same dietary regimen. The patient had, over time, what she and her physician considered complete resolution of fibromyalgia symptoms. The carpal tunnel symptoms disappeared, she began to sleep better, and believed that her memory improved as well. The patient rechallenged herself with

the food products she felt were the offending agents, and the symptoms returned. She restricted her diet again, and the symptoms resolved.

CASE 2

A 37-year-old white woman, the sister of the patient described above, had multiple medical problems including fibromyalgia syndrome affecting all 18 tender points, allergic rhinitis, irritable bowel syndrome, dysuria, stress reaction, depressive disorder, temperomandibular joint (TMJ) disorder, facial pain, carpal tunnel syndrome, anxiety, mitral valve prolapse, and dyslexia. She underwent a total hysterectomy in 1991 and surgery to open her left nasal passage. This woman was in a basically nonfunctional condition, much worse than her sister. She reported pains she had experienced since she was 15 years old. She did not recall a traumatic or emotional event prior to the onset of the pain.

The pains progressively worsened, especially after the birth of her first child in 1979, and never completely resolved. She underwent several tender point injections with bupivacaine, with temporary relief. The patient then began a corn-free diet and was able to decrease her amitriptyline dose from 100 to 25 mg/d and discontinue sertraline and lorazepam. After several months of using a diet free of aspartame and MSG, she had no pain in any of the tender points, no further abdominal or facial pain, no carpal tunnel syndrome, and no further depression or anxiety; a reevaluation also showed no sign of dyslexia. The woman also reported improvement in her memory. Symptoms of fibromyalgia recur when she unknowingly eats foods that contain MSG or aspartame. At times, she experiences an episode for 24–48 hours, and then researches if anything in her foods could have caused it. She often calls a food manufacturer to learn more details about the ingredients. Both the number of medications and number of office visits were markedly reduced after elimination of aspartame and MSG. On reevaluation, she had no further findings consistent with fibromyalgia, allergic rhinitis, irritable bowel syndrome, dysuria, stress reaction, chronic depressive disorder, TMJ disorder, or chronic fatigue issues.

CASE 3

A 57-year-old white woman had a past medical history of chronic musculoskeletal pain (very diffuse), chronic fatigue, migraine and tension headaches, irritable bowel syndrome, allergic rhinitis, gastroesophageal reflux disease, anxiety and depressive disorder, as well as a diagnosis in 1994 of fibromyalgia syndrome involving 16 of 18 tender points. Despite a major workup and extensive therapies, including physical therapy, electro-acupuncture, chiropractic treatment, injection treatment, counseling, medication, and lifestyle adjustment, her condition severely worsened, and she was placed on a diet to eliminate MSG and aspartame.

Within two months, she improved partially with no further headaches, allergic symptoms, or irritable bowel syndrome symptoms. Within three months, she had no further diffuse musculoskeletal pain and only continued to have very localized lower back and bilateral shoulder pain attributed to osteoarthritis. By seven months, she experienced no pain, but had achieved marked improvement of the chronic fatigue, and reported feeling "very good." If she inadvertently uses MSG, the symptoms recur. The number of medications she takes was reduced from 15 to only estrogen for hormone replacement.

CASE 4

A 37-year-old African-American woman was diagnosed with fibromyalgia syndrome involving all 18 tender points in 1985. Furthermore, she had ongoing diffuse multiple symptoms including severe fatigue, epigastric pain, retrosternal pain, precordial pains, symptoms consistent with some reflux (none could be substantiated with a 24-h pH study), major depressive episodes, chronic migraine and tension headaches, chronic musculoskeletal pain with costochondritis and myofacial pain component, chronic TMJ dysfunction, emphysema, chronic postnasal drip, hypercholesterolemia, hypertriglyceridemia, and obesity. At that time, she was receiving fluoxetine, triamterene/hydrochlorothiazide, nasal triamcinolone, fluticasone metered-dose inhaler (MDI), ipratroprium bromide MDI, albuterol MDI as needed, ranitidine twice daily, isosorbide dinitrate, buspirone, lorazepam, simvastatin, and propoxyphene/acetaminophen, along with repeated trigger point injections of bupivacaine.

The patient was told to try to eliminate MSG from her diet. After two months, she stated that she had improved dramatically. The headaches, as well as shoulder, neck, and abdominal pain, decreased from 8 of 10 to 3 of 10 in severity. After another month of elimination of MSG, the woman experienced even further pain improvement and believed that she was at 70% of her normal health. Her ranitidine dose was cut to once daily, the buspirone dose was decreased by half, propoxyphene/acetaminophen use decreased, and isosorbide dinitrate was discontinued. Secondary to her financial situation, she was unable to adjust her diet completely; whenever she uses certain foods, especially those that include MSG, she develops recurrent pain. She intermittently tried to stop buspirone completely, but felt very anxious and restarted the medication.

Table 1. Fibromyalgia Symptoms[1,3]

Symptoms	Prevalence (%)
Pain	
widespread	98
neck	85
low back	79
posterior thorax	72
≥15 painful sites	56
headache	53
dysmenorrhea	41
Other	
fatigue	81
morning stiffness >15 min	77
sleep disturbance	75
paresthesias	63
anxiety	48
dry mouth	36
prior depression	31
irritable bowel syndrome	30
urinary urgency	26
Raynaud's phenomenon	17

Discussion

MSG, the sodium salt of the amino acid glutamic acid or glutamate, is an additive used to enhance the flavor of certain foods. It does not have a flavor of its own, but is believed to enhance the taste of other foods by stimulating glutamate receptors on the tongue.

MSG was classified by the Food and Drug Administration (FDA) as a generally recognized as safe (GRAS) substance in 1959, after the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act required approval for new food additives. This classification meant that MSG and other GRAS substances, such as salt and baking powder, were grandfathered as harmless food substances due to their history of safe use. Since then, several expert committees have investigated MSG and determined that it is safe for use by the general public.[7-9]

Between 1980 and 1994, the Adverse Reaction Monitoring System in the FDA's Center for Food Safety and Applied Nutrition received 600 reports of problems due to MSG. Complaints, since verified in susceptible individuals,[10] included symptoms such as headache, weakness, muscle tightness, numbness or tingling, and flushing. Collectively, these symptoms have been termed the MSG symptom complex. The complaints submitted to the FDA, several books, and a television news show reporting the possible dangers of MSG prompted a review of the safety of the additive by the Federation of American Societies for Experimental Biology (FASEB). The 1995 FASEB report[11] reaffirmed the FDA's belief that MSG and related substances are safe food additives for most people.

However, that report[11] identified two groups of people who may develop complications from MSG. One group may be intolerant of MSG when the substance is eaten in large quantities, and develop the MSG symptom complex. The second group contains patients with severe, poorly controlled asthma, whose asthma may worsen after they eat foods containing MSG, in addition to being prone to MSG symptom complex.

Aspartame was first marketed in 1981. It is a dipeptide of aspartate and phenylalanine used in foods, beverages, and drugs. In animal models, aspartame has been associated with an increased incidence of brain tumors.[12] Anecdotally, aspartame use in humans has been linked with headaches, seizures, dizziness, movement disorders, urticaria, angioedema, and anaphylaxis. However, in placebo-controlled trials, only the potential for headache has been verified, even among self-identified susceptible patients.[13]

With the discovery of excitatory amino acid (EAA) transmitter systems and identification of EAA receptor subtypes (*N*-methyl-D-aspartame [NMDA], kainic acid, and amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid) and their antagonists, it has become widely accepted that glutamate, aspartate, and other environmental substances have neurotoxic (excitotoxic) effects in the human nervous system.[14]

The adverse reactions to MSG have been theorized to be due to MSG's actions at glutamate receptors in glutamate-responsive tissues. Studies have shown that glutamate acts as a neurotransmitter in the brain, and abnormal function of glutamate receptors has been linked to neurologic disorders such as Alzheimer disease and Huntington's chorea.[15] Injections of glutamate in laboratory animals have resulted in damage to nerve cells in the brain.

Aspartate is equipotent to glutamate in destroying hypothalamic neurons and has additive neurotoxic effects when the two are combined. Aspartate is derived from the gut hydrolyzation of aspartame. It is a much more potent flavoring agent than glutamate and is, therefore, used in smaller doses. However, even in small amounts, aspartate has additive effects to any glutamate.[14]

Normally, people can consume large amounts of dietary glutamate, and the body can produce and eliminate glutamate efficiently. Glutamate is rapidly absorbed into the bloodstream after oral administration. In fact, when compared with mice and monkeys, humans demonstrated higher plasma peaks and AUCs after receiving MSG 150 mg/kg.[14] Glutamate crosses the blood–brain barrier only by active transport, and concentrations in the brain are kept low and independent of plasma concentrations. However, glutamate freely enters brain regions that lack blood–brain barriers (circumventricular organs, e.g., the hypothalamus). It has been shown[14] that glutamate can destroy circumventricular organ neurons by an excitotoxic mechanism (via the NMDA receptor) in all animal models appropriately tested (cats, chickens, guinea pigs, hamsters, mice, monkeys, rabbits). In fact, much of the research performed proving that glutamate was safe for human consumption may have been flawed. Tests using infant monkeys anesthetized these animals with phencyclidine, now known to inhibit the neurotoxic effects of glutamate on the hypothalamic neurons by its potent antagonism of the specific subtype of NMDA receptor.[14]

As the etiology of fibromyalgia remains unclear, it is difficult to pinpoint an exact role for glutamate in its exacerbation or induction. However, several potential hypotheses can be envisioned. For example, when glutamate enters the endocrine hypothalamus, it interacts with EAA receptors on the surface of the hypothalamic neurons, which then stimulate the release of hypophysiotrophic-releasing factors. These factors trigger the release of pituitary hormones into the general circulation, which can disturb hormonal biorhythms. The use of intravenous glutamate or related analogs in prepubertal monkeys induces a release of growth hormone, luteinizing hormone, and prolactin.[14] However, recent tests[16] in healthy adult humans showed no increases in pituitary or cortical hormones in response to orally administered MSG. These findings do not preclude the possibility that a different response might occur in subsets of fibromyalgia patients. Up to 35% of subjects with fibromyalgia in various studies demonstrate abnormal suppression to the nighttime administration of dexamethasone. Additionally, patients with fibromyalgia have reduced 24-hour free cortisol excretion in the urine, loss of diurnal variation of cortisol concentrations, and exaggerated adrenocorticotrophic hormone, but blunted cortisol response to administration of corticotropin-releasing hormone or to insulin-induced hypoglycemia, and reduced adrenocortical activation in response to exhaustive exercise.[17]

Another plausible explanation involves the role of glutamate in chronic pain sensitization.[18] Prolonged firing of certain peripheral nociceptor neurons causes release of glutamate. This acts on central NMDA receptors to produce chronic sensitization at the level of the spinal cord. Perhaps exogenous glutamate may act to produce similar sensitization in a small subset of patients. Alternatively, MSG may represent a specific chemical intolerance, yielding a fibromyalgia-like picture as a result of some cross-sensitization.[19] Without further prospective studies in susceptible patients, clarifying the mechanism of glutamate toxicity remains, at best, difficult.

Obviously, this case series does not establish a cause–effect relationship between excitotoxins and fibromyalgia

syndrome. The potential relationship is further complicated by the often inconsistent manner in which fibromyalgia syndrome is diagnosed and documented in common practice. However, the Naranjo probability scale[20] places this drug reaction in or near the probable range. As MSG is nearly ubiquitous in processed food, appearing under many names, including gelatin, hydrolyzed vegetable protein, textured protein, and yeast extract, most people in developed nations are exposed to it from a very young age. The general population has less exposure to aspartame. Nonetheless, it is the dominant artificial sweetener on the market, and has been since its approval in 1981. In the four patients reported here, the adverse reaction improved on discontinuation and reappeared under retrial. As the patient in case 4 reduced, but did not eliminate, MSG and symptoms were reduced but not eliminated, one may argue a dose–response effect. Still, prospective, placebo-controlled trials are needed to verify the finding.

Summary

As the mystery of fibromyalgia syndrome unfolds and the diagnosis gains greater acceptance and awareness in both the medical and lay communities, one should remember that multiple etiologies of this syndrome exist. Our four patients were diagnosed with fibromyalgia syndrome that met the typical criteria. All also had allergic rhinitis symptoms and responded to a diet of mainly MSG elimination, aspartame elimination, or both with resolution of their symptoms. This excitotoxin-induced or -exacerbated fibromyalgia could be due to the mechanisms described above, but other mechanisms may remain unknown. We also do not believe that sensitivity to MSG is the cause of all cases of fibromyalgia syndrome, as many of our patients have not responded to our recommendations of elimination of the excitotoxins.

There may also be many more yet unknown, or widely unrecognized, excitotoxins that could also cause fibromyalgia syndrome. Even in the patients described here, we cannot state unequivocally that MSG caused their fibromyalgia. However, elimination of MSG and/or aspartame did result in striking improvements in their symptoms. Identification of similar patients and much more research must be performed before definitive conclusions concerning causation can be made. This subgroup of fibromyalgia syndrome patients needs to be identified by physicians and other healthcare providers to initiate appropriate dietary adjustments that may lead to significant improvement of symptoms, and to further delineate the mechanisms involved in their sensitivity.

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Appendix I. American College of Rheumatology Diagnostic Criteria for Fibromyalgia[3]

History of Widespread Pain
considered widespread when all of the following sites of pain are present:
- left side of the body
- right side of the body
- above the waist
- below the waist
- axial skeleton (cervical spine or anterior chest or thoracic spine or low back)
- shoulder and buttock pain considered as pain for each involved site
- low back pain considered lower-segment pain

Pain on digital palpitation in 11 of the 18 (bilateral) following sites of tender points:
- occiput: suboccipital muscle insertions
- low cervical: anterior aspects of the intertransverse spaces at C5–C7
- trapezius: midpoint of the upper border
- supraspinatous: above the scapular spine near the medial border
- second rib: at the second costochondral junctions, just lateral to the junctions on the upper surfaces
- lateral epicondyle: 2 cm distal to the epicondyles
- gluteal: upper outer quadrants of buttocks in anterior fold of muscle
- greater trochanter: posterior to the trochanteric prominence
- knee: medial fat pad proximal to the joint line

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EXTRACTO

OBJETIVO: La fibromialgia es una afección reumática que muchas veces es dificil tratar efectivamente.

RESUMEN DEL CASO: Se describen cuatro pacientes con el síndrome de fibromialgia por una duración de dos a 17 años. Todas fueron tratatadas con varios tratamientos con poco éxito. En todas se observó completa o casi completa resolución de los síntomas en unos pocos meses después de eliminar el glutamato modosódico (MSG) ± aspartame de su dieta.

DISCUSIÓN: Las excitotoxinas son moléculas, como MSG y aspartato, que actuan como neurotransmisores excitatorios y que, en exceso, pueden causar neurotoxicidad. Los autores sugieren que las cuatro pacientes descritas representan un subconjunto de pacientes con síndrome de fibromialgia inducido u exacerbado por excitotoxinas o, alternativamente, un subconjunto con un síndrome de excitotoxina que es similar a la fibromialgia. La identificación de otros pacientes similares y mucho más estudio es necesario antes de llegar a conclusiones definitivas.

CONCLUSIONES: La eliminación de MSG y otras excitotoxinas de la dieta constituye una opción terapeútica para pacientes con fibromylagia. Este tratamiento benigno tiene el potencial para producir resultados positivos dramáticos en un subconjunto de pacientes.

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RÉSUMÉ

RÉSUMÉ DU CAS: Cet article décrit quatre cas de fibromyalgie pour une période de deux à 17 ans. Tous les patients ont reçu de nombreuses modalités de traitement avec des résultats limités. Cependant, tous les malades ont eu une résolution complète, ou presque complète, de leur symptômes dans les mois suivant l'élimination du glutamate monosodique (MSG) ± aspartame de leur alimentation. Ce sont toutes des femmes, atteintes de nombreux problèmes médicaux avant l'élimination du MSG. Toutes ont une recrudescence des symptômes à l'ingestion du MSG.

DISCUSSION: Les excitotoxines sont des molécules, telles que le MSG et l'aspartame, qui agissent sur les neurotransmetteurs excitatoires et qui peuvent conduire à une neurotoxicité excessive. L'hypothèse proposée ici est que ces quatre patientes puissent présenter une forme de syndrome de fibromyalgie induit ou exacerbé par les excitotoxines ou, alternativement, puissent comprendre un syndrome d'excitotoxine similaire à la fibromyalgie. L'identification d'autres patients avec des symptômes similaires ainsi qu'une recherche poussée sur un plus grand nombre de sujets doit être effectué avant qu'on ne tire de conclusions définitives.

CONCLUSIONS: L'élimination du MSG et des autres excitotoxines de la diète des patients atteints de fibromyalgie offre une option thérapeutique bénigne avec un potentiel de résultats impressionnants chez un certain nombre de sujets.

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