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Case Report

Inflammatory Bowel Disease, Iron Deficiency Anemia and Systemic Nickel Allergy Syndrome: What is the Significance of the Low Nickel Diet and Chronic *H. Pylori* Infection? A Case Report

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Received: July 25, 2017; **Published:** August 17, 2017

Abstract

A 33-year-old Caucasian female, previously diagnosed with ulcerative colitis (UC), presented with a five-year long history of severe gastrointestinal and extra-gastrointestinal manifestations, including iron deficiency anemia (IDA). She turned to clinical functional nutrition counseling after a series of conventional medical interventions failed to provide benefit. Recommendations for extensive laboratory evaluation were suggested (testing to identify heavy metal toxicity and environmental and/or food allergies/sensitivities), of which the patient opted to have food allergy/sensitivity testing. Laboratory testing revealed sensitivity to nickel-rich foods, which prompted a referral to an allergist and a diagnosis of systemic nickel allergy syndrome (SNAS). Additionally, a history of chronic, untreated *H. pylori* infection was revealed following a severe food poisoning approximately four years prior to the official UC diagnosis. The UC diagnosis was preceded by proctitis and pancolitis. Medical nutrition therapy included a low nickel diet, iron supplementation, and lifestyle recommendations. Within one week of initiating dietary interventions, there were improvements in gastrointestinal symptomatology. Due to patient's adverse reaction to IDA therapy, specifically iron supplementation, the extra-gastrointestinal manifestation, namely the IDA persists.

Keywords: *Inflammatory Bowel Disease; Iron Deficiency Anemia; Systemic Nickel Allergy Syndrome; H. Pylori; Low Nickel Diet; Medical Nutrition Therapy*

Background and Aim

The patient is a 33-year-old female who was diagnosed with ulcerative colitis (UC), a chronic inflammatory bowel disease (IBD), and presented with a five-year long history of severe gastrointestinal and extra-gastrointestinal manifestations, including iron deficiency anemia (IDA). She turned to clinical functional nutrition counseling after a series of conventional medical interventions failed to provide benefit. Recommendations for extensive lab evaluation were suggested (testing to identify heavy metal toxicity and environmental and/or food allergies/sensitivities), of which the patient opted to have food allergy/sensitivity testing. Laboratory testing revealed sensitivity to nickel-rich foods, which prompted a referral to an allergist and a diagnosis of systemic nickel allergy syndrome (SNAS). Additionally, a history of chronic, untreated *H. pylori* infection was revealed following a severe food poisoning approximately four years prior to the official UC diagnosis. The UC diagnosis was preceded by proctitis and pancolitis. Medical nutrition therapy included a low nickel diet, iron supplementation, and lifestyle recommendations. This case was rather challenging as a result of several factors: a full history only emerged over time (multiple visits), case assessment was complicated by the number of comorbidities and the severity thereof, limitations in access to laboratory testing in the region where the patient resides and poor coordination of care as a result of differing practice paradigms among the patient's care team. Within one week of initiating dietary interventions, there were improvements in gastrointestinal symptomatology, however her extra-gastrointestinal manifestation, namely the IDA persists. Further testing to identify potential heavy metal toxicity and viral infection(s) have been recommended. Addressing nutritional status such as clinical iron and vitamin D deficiencies is the next intervention goal.

Case Presentation

This case has an extensive history of triggering events and the patient's most current condition may be related to the sequential order of the events (see Appendix 1: Timeline of the Events).

Food Poisonings and *H. pylori* Infection

Patient contracted an *H. pylori* infection in 2011 via a food poisoning, which was not treated. Following the food poisoning she developed chronic diarrhea. She relocated twice between 2012 and 2013; first to Japan and then to San Diego, CA and changed her diet each time she moved. She then had a repeat food poisoning in late 2013 while in San Diego. This time she developed bloody, watery diarrhea and lost 30 pounds within one month.

Proctitis and Pancolitis Diagnoses, Poor Response to Medication, Extra-Gastrointestinal Manifestations

Proctitis was diagnosed via colonoscopy and Lialda medication was prescribed. She reacted poorly to the medication with worsening of bloody watery diarrhea which resolved after she stopped taking the medication. A year later, in the fall of 2014, she was hospitalized with severe dehydration, anemia, hallucinations, and heavy rectal bleeding of up to three cups of blood per day and diarrhea up to 25 times per day. This time she was diagnosed with pancolitis and hydrocortisone treatment was administered at the hospital and prednisone was prescribed. Patient took prednisone for ten days while her gastrointestinal symptoms continued to worsen. Additionally, she developed extra-gastrointestinal symptoms including sensitivity to vibrations and hand tremors. She stopped taking prednisone and began taking hydrocortisone which resulted in slight improvements in extra-gastrointestinal symptoms while the diarrhea continued. Her weight decreased to 95 pounds.

Exogenous Cushing's Syndrome and Ulcerative Colitis Diagnosis

Hydrocortisone induced exogenous Cushing's Syndrome. A month later she was hospitalized once more and diagnosed with ulcerative colitis (UC). Hydrocortisone and tramadol were prescribed in mid 2015 and for the next month she was on bed rest, unable to walk due to the iron deficiency anemia (IDA). A new medication was prescribed (6-MP Mercaptopurine), however it resulted in severe vomiting and patient was unable to continue with treatment despite of her doctor advising for her to stay patient as the medication generally takes six months to start working. Within the next month, she developed severe anxiety and trouble breathing. She was also unable to leave her house due to the anxiety level. Biologics via transfusion were proposed by her doctor, however she declined the treatment. New symptoms developed including head, hand and the entire body tremors, which prompted her to meet with a neurologist. Various tests including magnetic resonance imaging and blood work were inconclusive. She tapered off of hydrocortisone. Her bloody diarrhea improved, however she was experiencing severe fatigue. Self-monitored ten day cleanse was followed by an emergency room (ER) visit with difficulty breathing and severe chest and lower back pain in late 2015. Chest X-Ray and electrocardiogram revealed no abnormal findings, however the blood work revealed leukocytosis.

Pyodema Gangrenosum Diagnosis, Poor Response to Medication and Foot Surgeries

Nine days later she was back in the ER at a different hospital with foot pain, erythema, and swelling of the right foot. Her hemoglobin was severely low and her status required a blood transfusion, which was performed. She was admitted to the hospital overnight and discharged the next morning without further instructions. Patient was back in the ER several days later and a hairline fracture was suspected. Oxycodone was administered; she lost consciousness a few minutes after the medication was administered. This event resulted from an overdose as the medication dose was not properly calculated for her weight. She was discharged and about a week later had to call an ambulance to get her to the ER once again. Patient experienced cyanosis of her right foot and unbearable foot pain. Pyodema gangrenosum was diagnosed and vancomycin was administered; followed by surgical debridement of a soft tissue infection in the medial aspect of the hindfoot two days later.

Ulcerative Colitis Short Term Remissions with Vancomycin and Relapse

Vancomycin resolved the UC symptoms. For the next four months she was not taking any antibiotics and in April 2015 her UC symptoms returned. Hydrocortisone was prescribed again and she developed dyspnea for three days (which resolved on its own). Her foot pain returned in April of 2016 and she took Vancomycin for 60 days, which resolved the UC symptoms, and she was able to eat without pain thereafter. A second foot surgery was performed and ten days after stopping the vancomycin the UC symptoms returned again. In June 2016 she started two new medications: Cipro and Flagyl which helped to ease the pain, however the bleeding continued. After ten days on the new medication, it became too painful for her to eat any food.

Systemic Nickel Allergy Syndrome Diagnosis, Low Nickel Diet and Lifestyle Changes

In July 2016 she met with a nutritionist who recommended heavy metal toxicity and environmental allergies/sensitivities testing via ELISA-LRA all-inclusive test. Patient decided to pursue the food sensitivity testing - which revealed sensitivity to seven foods all high in nickel (Ni) content (see Appendix 2: ELISA/ACT-LRA Results). This prompted a recommendation by a nutritionist to see an allergist for further testing. An allergist diagnosed systemic nickel allergy syndrome (SNAS) via skin patch and serum testing. A low nickel and low sulfate diet as well as lifestyle recommendations were recommended (see Nutrition and Lifestyle Changes Patient Made to Limit Nickel Exposure/Intake).

Ulcerative Colitis Symptoms Remission

One week after she commenced the nutrition and lifestyle changes (see Appendix 4: Low Nickel Nutrition and Lifestyle Changes) in December of 2016, her UC symptoms resolved. She reported being free of symptoms, hospitalizations and medications for 100 days in April of 2017. Her most recent blood work in May of 2017 revealed zero Ni in the serum, however her other serum markers did not improve significantly (see Appendix 3: Laboratory Data). She is due for repeat blood work and colonoscopy in September 2017.

Persisting Iron Deficiency Anemia and Remaining Case Challenges

Her persisting IDA and vitamin D deficiency is of a great concern even though her UC has been in remission for the past seven months. She is currently continuing with all of the previous nutrition and lifestyle changes. An attempt at oral iron supplementation resulted in a return of rectal bleeding and the patient is afraid to continue to take supplemental iron. Her treating doctor is unsure how to proceed with the case and thus no alternative IDA treatment is being proposed by her medical team at this time. Nutritionist's recommendations included a trial of whole foods-based blood building supplement, which the patient refused, stating that she is unable to tolerate "anything made with vegetables and green except for cucumbers and zucchini." Additionally, she expressed concern with vitamin D supplementation as well. She takes 5,000 IU q.d. however inconsistently due to the belief that "anything manufactured potentially has nickel in it from either the machines or the steel tanks holding tanks." The challenges of this case at this point in time lies in the patient's fear to proceed with the proposed interventions (to correct iron and vitamin D deficiencies) as well as her medical team's lack of plan of care.

Conclusions

Helicobacter pylori and Nickel Connection

Ni is required for two enzymes: hydrogenase and urease, important in colonization of gastric mucosa. The study conducted by Benoit, Miller and Maier indicated that *Helicobacter pylori* (*H. pylori*) can utilize Ni in order to aid colonization of the host. Nickel is a key metal for the gastric pathogen *H. pylori* and since it is non-essential for humans (as a catalyst or cofactor), there is no competing factor between the human host and the bacterium, making nickel abundant for *H. pylori* use. When the host is not consuming a diet rich in nickel, *H. pylori* relies on storage levels of nickel via intracellular nickel reservoir [1]. Since the patient was consuming diet high in nickel, it is speculated that a perfect environment was created for the *H. pylori* colonization. Additionally, the infection was left untreated allowing for further pathogenesis of IBD.

Inflammatory Bowel Disease and *H. pylori* Connection

H. pylori is a Gram-negative spiral-shaped pathogenic bacterium and its role in the etiology of gastric and duodenal ulceration is well-studied. It is a primary cause of peptic and gastric cancer and is classified as a group I carcinogen by the International Agency for Research on Cancer [2]. Two subgroups of *H. pylori* exist: gastric helicobacter (localized in the stomach) and enterohepatic helicobacter (localized in intestinal and hepatobiliary system) [3]. The role of *H. pylori* in extragastric disease pathophysiology is significantly underappreciated. Moreover, *H. pylori* virulence factors depend upon the presence or absence of multiple metal ions including nickel, iron, copper and zinc in the stomach and within tissues of the host [4]. *H. pylori* infection triggers the inflammatory and immune response in the host [5].

Iron Deficiency Anemia, Inflammatory Bowel Disease and Nickel Connection

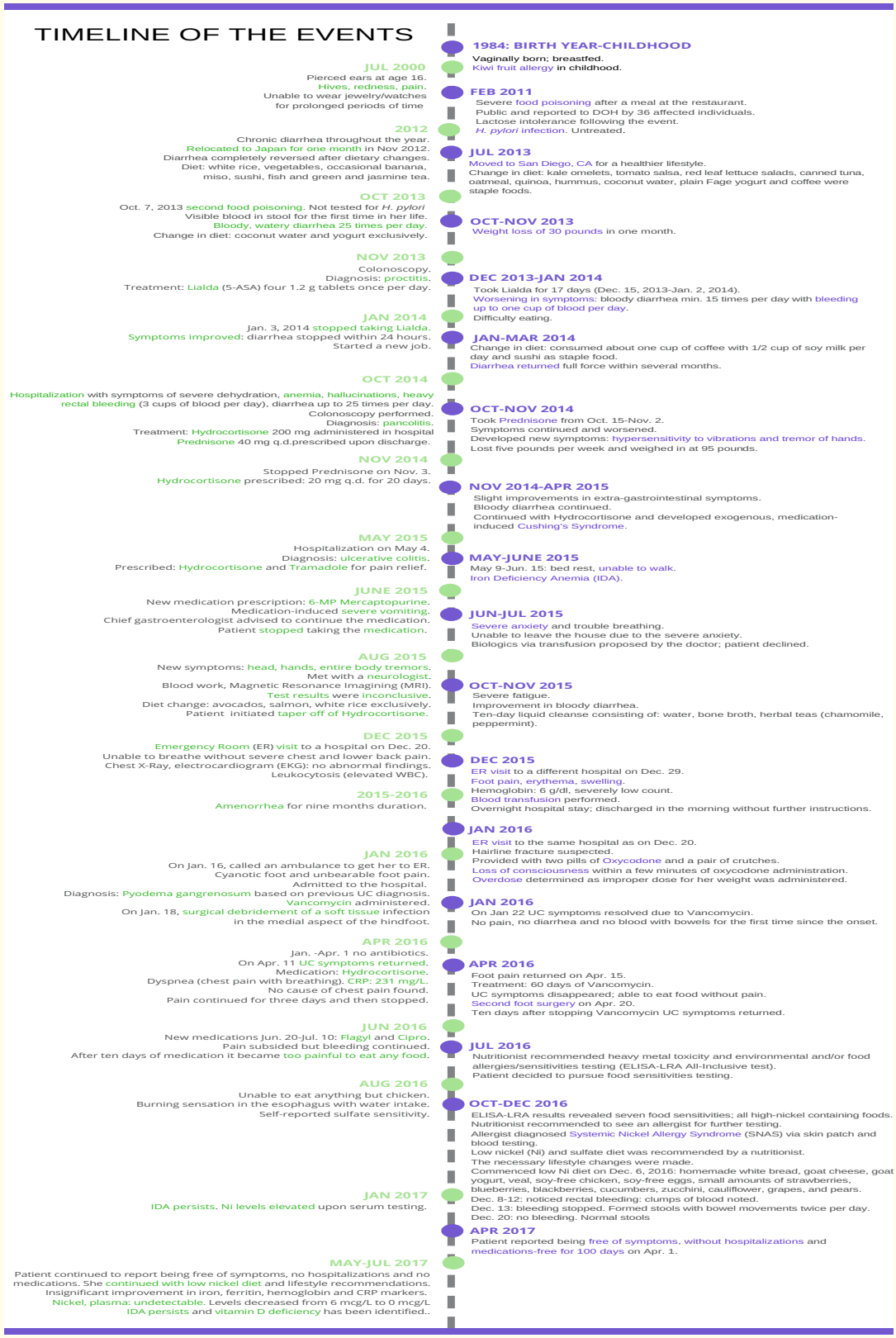
"Iron deficiency occurs in 60 - 80% of patients with inflammatory bowel disease (IBD), and iron deficiency anemia manifests in approximately one-third of patients with IBD". Anemia is thus by far the most common extraintestinal complication of IBD [6]. Iron absorption is decreased in IBD and the goal for the patient is to have an individualized, tolerable treatment for IDA [7]. Interestingly, IDA can enhance nickel absorption and thus adequate iron intake and iron status is critical to effectively treating (or managing) this condition [8,9]. Vitamin C, tea, coffee, and milk inhibit absorption of nickel (also see Appendix 5: Nickel-Rich Foods which shall be limited or avoided). Binding or chelating substances, redox reagents, or competitive inhibitors may also reduce the absorption of nickel.

The Role of Low Nickel Diet

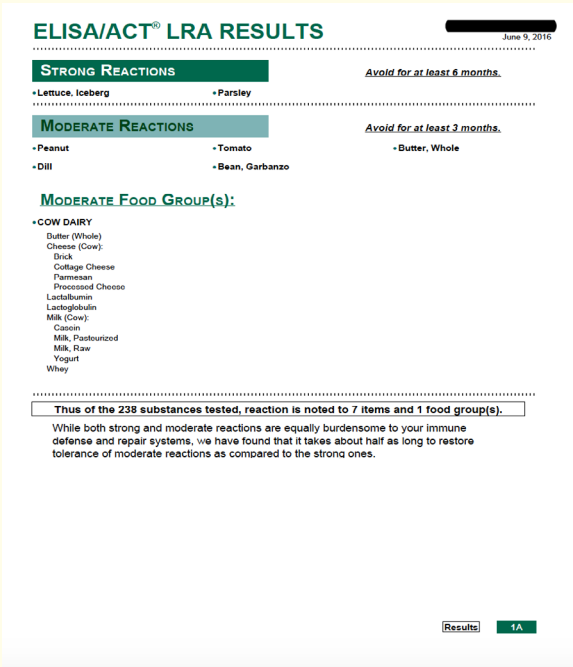
A low nickel diet is indicated for Systemic Nickel Allergy Syndrome, contact dermatitis, and gastrointestinal manifestations related to nickel allergy. A low nickel diet may improve the systemic manifestations of SNAS by limiting gastrointestinal symptoms and improving the quality of life and psychological status of Ni-sensitized individuals [10-18].

Acknowledgement

Dr. Dana Filatova would like to acknowledge the support and guidance of her mentor, Dr. Mary Fry, N.D.



Appendix 1: *Timeline of the Events.*



ELISA/ACT® LRA RESULTS

[redacted]
June 9, 2016

STRONG REACTIONS — *Avoid for at least 6 months.*

- Lettuce, Iceberg
- Parsley

MODERATE REACTIONS — *Avoid for at least 3 months.*

- Peanut
- Tomato
- Butter, Whole
- Dill
- Bean, Garbanzo

MODERATE FOOD GROUP(S):

- COW DAIRY
  - Butter (Whole)
  - Cheese (Cow):
    - Brick
    - Cottage Cheese
    - Parmesan
    - Processed Cheese
  - Lactalbumin
  - Lactoglobulin
  - Milk (Cow):
    - Casein
    - Milk, Pasteurized
    - Milk, Raw
    - Yogurt
  - Whey

Thus of the 238 substances tested, reaction is noted to 7 items and 1 food group(s).

While both strong and moderate reactions are equally burdensome to your immune defense and repair systems, we have found that it takes about half as long to restore tolerance of moderate reactions as compared to the strong ones.

Results 1A

Appendix 2: *ELISA/ACT-LRA results.*

	4/14/16	6/14/16	7/7/16	8/12/16	9/16/16	1/9/17	2/10/17	5/5/17
Iron	26 ug/dl TIBC: 328 Ug/dl	n/a	n/a	n/a	16 ug/dL	29 ug/dL	17 ug/dL	31 ug/dl
Ferritin	8.4 ng/nl	n/a	n/a	n/a	29 ng/nL	3 ng/nL	2 ng/nL	3 ng/nL
Hemoglobin	13.2 g/dL	8.2 g/dL	9.1 g/dL	11.7 g/dL	11.7 g/dL	11.8 g/dL	12.1 g/dL	12.5 g/dL
Hematocrit	38.10%	38%	37.5%	37.3%	29.5%	26.2%	42%	38.7%
RBC	4.67 m/uL	4.55 m/uL	4.29 m/uL	4.48 m/uL	3.55 m/uL	3.2 m/uL	4.88 m/uL	4.55 m/uL
RDW	14.1%	14%	20.7%	16.7%	18%	16.3%	15.5%	15.6%
CRP	n/a	231 mg/L	7/7/16 Hs-CRP: 1.7 mg/L	7/7/16: 2.0 mg/L	5.98 mg/L	2.62 mg/L	5.21 mg/L	2.97 mg/L
Sed Rate (ESR)	n/a	n/a	32 mm/hr	33 mm/hr	44 mm/hr	23 mm/hr	28 mm/hr	13 mm/hr
Glucose	62 mg/dl HgbA1C: 5.4%	n/a	70 mg/dL	66 mg/dL	67 mg/dl	48 mg/dl	n/a	75 mg/dl
25(OH)D	47.9 ng/mL	n/a	n/a	n/a	32.4 ng/mL	n/a	n/a	20.8 ng/m
Folate	n/a	n/a	n/a	n/a	16.8 nglmL	n/a	n/a	10.51 ng/ml
B12	616 pg/mL	n/a	n/a	n/a	603 pg/mL	n/a	n/a	275 pg/mL MMA: 0.18 umol/L
MTHFR	Heterozygous for C665C > T and negative for C1286A > C							

Appendix 3: *Laboratory Data.*

NUTRITION & LIFESTYLE CHANGES PATIENT MADE TO LIMIT NICKEL EXPOSURE / INTAKE

1. Changed all pots and pans to cast iron coated with ceramic.
2. Switched to distilled water and *SmartWater.*
3. Consumes a diet of no more than 1 mg of nickel per day using the FDA list of nickel-containing foods.
4. Avoids eating at restaurants. If eating at friend's house, brings a meal with her.
5. Switched washing machine tablets to *Method* brand - unscented.
6. Switched laundry detergent to *Arm & Hammer* - unscented.
7. Stopped using aluminum foil and started using parchment paper.
8. Switched deodorant to aluminum-free *Tom's of Maine*.
9. Put all keys in silicone wrappers.
10. Uses sleeves to open all kitchen cabinets, doors, and to turn on faucets, etc.
11. Eats small amount of vitamin C-rich blueberries with all meals.
12. Avoids citrus fruits.
13. Installed a protective tempered glass screen on the mobile phone to avoid skin contact with mobile device material and potential nickel exposure.
14. Washes all new clothes twice with hypoallergenic laundry detergent to avoid nickel-containing formaldehyde.
15. Runs shower water for 15 minutes prior to getting into the shower to avoid nickel from the pipes.
16. Switched to a sulfate-free and nickel-free shampoo.
17. Stopped using mica-containing skin and decorative cosmetics.
18. Started using chopsticks instead of utensils.
19. Stopped purchasing foods packages in metal containers.
20. Avoids all foods grown in volcanic soils (foods originating from Hawaii for example).

Appendix 4: *Low Nickel Nutrition and Lifestyle Changes.*

Nickel-rich Foods			
Ni 100 µg/kg	**Ni 200 µg/kg**	**Ni 500 µg/kg**	**Ni > 500 µg/kg**
Carrots	Apricots	Artichoke	Almonds
Figs	Broccoli	Asparagus	Chickpeas
Lettuce	Corn	Beans	Cocoa
Green salad	Lobster	Cabbage	Concentrated tomato
Licorice	Onions	Cauliflower	Lentils
Mushrooms	Pears	Green beans	Oats
Plaice and cod	Raisins	Integral flour	Peanuts
Rhubarb		Yeast	Walnuts
Tea		Margarine	
		Mussels	
		Oysters	
		Potatoes	
		Peas	
		Plums	
		Spinach	
		Tomatoes	

Appendix 5: *Nickel-Rich Foods.*

Adapted from Rizzi A., et al. "Irritable bowel syndrome and nickel allergy: What is the role of the low nickel diet?" Journal of Neurogastroenterology and Motility 23.1 (2017): 101-108.

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Volume 10 Issue 3 August 2017