

CASE REPORT

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Levonorgestrel-Releasing Intrauterine System and Iron Overload Syndrome

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Abstract: Severe fatigue is a common complaint among patients. This report presents a clinical case of a woman complaining of fatigue associated with diarrhea and myalgia that were first attributed to emotional stress and depression. Initially, the patient was diagnosed with chronic fatigue and irritable bowel syndrome. The patient followed nutritional and physical exercise programs without any improvement. Other clinical conditions, such as nutritional deficiencies, endocrine dysfunctions, autoimmune diseases and neoplasias, were then assessed. During clinical investigation, serum ferritin and iron levels were abnormally elevated despite normal hemoglobin levels, which pointed to an iron overload syndrome later diagnosed as hemochromatosis. It is possible that the symptoms were triggered by the amenorrhea caused by the levonorgestrel-releasing intrauterine system used for contraception.

Keywords: hemochromatosis, iron overload, hormone releasing IUD/contraindications

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Clinical Case

A 41-year-old Caucasian woman complaining of persistent diarrhea, diffuse neck myalgia, swollen fingers and fatigue was clinically evaluated.

Early morning fatigue and continuous neck pain started 6 months earlier and were initially attributed to stress by the patient's regular physician, who recommended psychotherapy. These symptoms did not improve and were worsened after a crisis of gastroenteritis due to seafood, associated with fever and severe abdominal pain, which resolved in 2 days. Despite improvement of the acute gastroenteritis, an intermittent diarrhea, without mucous or blood, persisted for another 2 months while the patient developed swollen fingers and a sudden outbreak of acne.

The patient's clinical history revealed that she had pre-eclampsia during her only pregnancy (9 years earlier), mumps and pancreatitis at 9 years old, and a myalgic crisis 4 years earlier, diagnosed at the time as fibromyalgia by her orthopedist. She had never smoked and was not under any medical treatment except for contraception with a levonorgestrel-releasing (20 mcg/day) intrauterine system for the previous 5 years with complete amenorrhea. The myalgic episode was resolved with cyclobenzaprine hydrochloride (15 mg/day) and a healthy sleep routine. Family history revealed that her father died of glioblastoma multiforme (GBM) and her grandfather died of abdominal cancer of unknown origin.

The only finding from the physical examination was a discrete tenderness upon palpation of the liver. Hematological values were within normal range. She presented with borderline high levels of LDL, HDL and total cholesterol (138 mg/dL, 48 mg/dL and 207 mg/dL). Triglyceride and VLDL cholesterol levels were 104 mg/dL and 21 mg/dL, respectively. The values for serum apolipoprotein A1 and B were 125 and 106 mg/dL, respectively. The patient tested negative for enteric parasites and fecal occult blood. Urinalysis revealed normal findings.

Except for a slightly elevated gamma-GT (88 U/L), all hepatic parameters were within normal limits. Thyroid ultrasonography revealed a colloid cyst in the right lobe, but the TSH, free T3 and T4 levels were normal. Although her fasting glucose was within normal limits, the patient presented with 2-hour post-challenge hyperglycemia (2 hPG > 140 mg/dL), which was suggestive of impaired glucose tolerance.

The HbA_{1c} value was 5.4%. The seric amylase level was 97 U/L and the lipase level was 42 U/L. The urea, creatinine, and electrolytes (Ca, inorganic P, Na, K and Mg) values were normal. Plasma ACTH was 9 pg/mL, serum GHG was 0.61 mg/L, cortisol levels were 8.5 and 7.7 mg/dL at 8 am and 4 pm, respectively, DHEA was 400 ng/dL and DHEA-s was 230 µg/dL.

Immunological investigation was positive for the following autoantibodies: ANAs ($\geq 1/320$ —nuclear and metaphasic chromosome, $\geq 1/160$ —cytoplasmic) and anti-smooth muscle. The panel was negative for p-ANCA, c-ANCA, CEA, Ca 19-9, ANA (nucleolar and nuclear mitotic apparatus), anti-nucleosome, anti-Sm, anti-RNP, anti-thyroglobulin, anti-thyroid peroxidase and native DNA. Serum levels of folic acid (327 ng/mL), vitamin B12 (438 ng/L), 25 hydroxyvitamin D (23 ng/mL) and 1, 25 dihydroxyvitamin D (42 pg/mL) were within normal ranges. The testosterone level was 34 ng/dL.

The echocardiogram was normal. Abdominal and pelvic ultrasonographies were normal except for a discrete increase in liver lipid infiltration. The intra-uterine device was adequately positioned.

At this point, a dietary intervention (a low carbohydrate diet with lactose restriction) was prescribed, and the patient started a physical outdoor exercise program (50 minutes of walking, 5 times a week). Further immunologic testing was performed, but the results were either negative or normal (anti-mitochondrial antibody, Ro/SS-A antigen, La/SS-B antigen, serum immunoelectrophoresis, seric proteins electrophoresis, and serum IgA, IgG and IgM levels). During the following 5 months, the impaired glucose tolerance was controlled (2 hPG = 132 mg/dL), and she lost approximately 13 pounds (lb; starting weight: 156 lb, 5'8"); the diarrheic episodes diminished, but the fatigue persisted. The acne outbreaks were resolved with antibiotic therapy (tetracycline, 1 g/day, for 2 months). Family and colleagues ruled out personal and social problems. The physical exam was normal, and further laboratory tests were obtained.

Blood hematological parameters remained unremarkable, but at this time, serum ferritin was assessed. The elevated levels (216 mg/L) indicated that the patient most likely had an iron overload syndrome. She was screened for C282Y, H63D and S65C mutations and was homozygous positive for H63D. Abdominal magnetic resonance image (MRI)



confirmed a hepatic iron overload of 50 $\mu\text{mol/g}$ with a standard deviation of 30 $\mu\text{mol/g}$.

The patient was referred to a hepatologist who prescribed 4 therapeutic bleedings (phlebotomies) of 500 mL, once a month for 4 months. The intrauterine device was removed to restart menstruation and allow for natural iron loss. Initially, the patient experienced extensive extremities edema, decreased immunological resistance and some dizziness after the phlebotomies. Diarrheic episodes ceased, and the fatigue decreased. Regular monthly menses were established after 2 months, and there was an increase in libido, although this was not a previous complaint. After all the phlebotomies, the serum ferritin levels returned to normal (52 $\mu\text{g/L}$) and the abdominal MRI findings showed a decrease in the hepatic iron concentration (40 $\mu\text{mol/g}$, standard deviation of 30 $\mu\text{mol/g}$).

Differential Diagnosis: Gastroenterological signs and symptoms

This patient most likely has had food-borne infectious diarrhea from eating raw shellfish, but its unusual persistence suggested that other problems were involved. The differential diagnosis of these infections is wide, ranging from viral infections to parasitic infections. Parasites were ruled out by the stool exam; however, no culture was performed, which might have been helpful. The symptoms persisted for over 4 weeks and were consistent with chronic diarrhea, which is mostly non-infectious in nature. She was afebrile, with normal blood pressure, with neither lymphadenopathy nor a tender abdomen, and had normal bowel sounds. Chronic diarrhea and watery stools are suggestive of chronic and inflammatory conditions that may compromise the small bowel (eg, lactose intolerance, malabsorption syndromes, infections such as *Shigella sp.*, *Salmonella sp.*, *Yersinia sp.*, and *Escherichia coli*, pancreatic diseases, bile salt-deficiencies) and colon (eg, inflammatory bowel disease, irritable bowel syndrome, infections, Crohn's disease).¹ In healthy persons, for example, *Yersinia enterocolitica* seems relatively avirulent, but with increased iron availability, the infection can develop into septicemia or be persistent for months. The episodes in this case ceased while the patient was under the dietary intervention for the impaired glucose tolerance and taking high doses

of tetracycline for the acne outbreaks. The glucose intolerance and the antigenic findings observed in the first set of exams pointed toward a different direction, so the original gastrointestinal infection was not further pursued.

Fatigue Symptoms and Depression

The patient's complaint of fatigue was further investigated by assessing a wide range of clinical conditions such as nutritional deficiencies (serum levels of vitamin D, B12, and folic acid), endocrine dysfunctions (adrenal insufficiency, Cushing's syndrome, diabetes, hyperparathyroidism, testosterone deficiency, thyroid dysfunction), anemia, and even neoplasias. Stressful life events, such as loss of a family member, a job or a spouse, have all been associated with health deterioration and depression. However, clinicians should not readily rule out a systemic origin for fatigue when symptoms of depression are present.² In fact, the first set of exams of this patient pointed to glucose intolerance and some immunological alterations. Both diabetes and impaired glucose tolerance have been previously associated with depression by unknown mechanisms.³

Glucose Intolerance

Impaired glucose tolerance (IGT) is a known risk factor for diabetes and for heart disease. It occurs in 15.6% of adults at 40 to 74 years of age⁴ and is diagnosed through a glucose tolerance test. This patient had a history of increased weight gain during pregnancy (88 lb) due to pre-eclampsia (no gestational diabetes), but otherwise had no weight problem (132.2 lb, 5'8"). There was no family history of diabetes.

IGT increased the suspicions of impaired insulin release that could be associated with storage diseases, such as iron overload—confirmed in this case with the elevated serum ferritin levels. Pancreatic iron overload may cause insulin release impairment if not treated.⁵ A reduced carbohydrate diet and physical exercise were the first steps in dealing with this condition and proved to be adequate for this clinical scenario. It is likely that this patient's IGT benefited not only from her eating habit changes and her improvement in physical conditions, but also from the phlebotomies, which decreased the hepatic iron deposits as observed in the MRI images. Non-invasive assessment of hepatic iron



stores by MRI avoids unnecessary hepatic biopsy and its complications.

Rheumatological Complaints

The joint discomfort was suggestive of inflammatory arthritis that could be have been related to a rheumatic disorder or a non-rheumatic systemic disease, such as inflammatory bowel disease. The patient had increased levels of antinuclear and anti-smooth antibodies, as well as symptoms easily attributed to fibromyalgia. Joint pain complaints are referred to in storage syndromes such as iron overload, mimicking rheumatological disorders that should be considered in the differential diagnosis. This patient had unspecific symptoms except for eventual swollen proximal interphalangeal joints and neck myalgia. Additional exams were conducted to rule out a series of autoimmune diseases and all were within normal parameters.

Discussion

Women have numerous choices for contraceptive methods, including some that avoid menstruation (necessary for therapeutic reasons or fitted for personal preferences), such as the levonorgestrel-releasing intrauterine system (IUS). It is an effective form of long-term reversible birth control that, by causing amenorrhea, may have a significant impact in populations where iron deficiencies are endemic. In a study conducted in India, women evaluated in terms of menstrual bleeding patterns and blood elements parameters after insertion of an IUS and copper-releasing intrauterine device (IUD) indicated that serum ferritin, hemoglobin concentration, menstrual bleeding and spotting days were significantly different depending upon the device type. Both groups presented increased bleeding days during the months following insertion, but after a 12-month period, women using IUS presented with a significant rise in hemoglobin and serum ferritin levels in addition to a reduced number of menstrual bleeding days. The authors concluded that the IUS was a relevant contraceptive method that could improve health conditions in populations facing iron deficient situations, such as those of developing countries.⁶ Similar results and conclusions were previously reported in Brazil, reinforcing the importance of the levonorgestrel-releasing intrauterine system in terms of preventing anemia.⁷

Alternatively, by stressing the relevance of the IUS in preventing body iron loss, these data also suggest that it could be harmful in situations where the patient presents with health conditions related to iron overload, such as in the present case.

The non-specific nature of early hemochromatosis symptoms usually delays the diagnosis, unless the family history triggers genetic or laboratory testing. In the initial stages, symptoms are non-specific and may evolve to manifestations, at an older age, of diabetes mellitus, hypogonadism, arthralgias, osteoporosis, cirrhosis, hepatocellular cancer, or cardiomyopathy. The clinical disease is less common in women due to physiological blood loss from menstruation and pregnancy.

The benefits of blood loss in women with hereditary hemochromatosis are supported by the fact that iron overload symptoms commonly start after menopause.⁸ This should be considered whenever clinical or medical interventions that cause amenorrhea are implemented for women at risk of iron overload syndromes or must be considered whenever symptoms such as these are reported in situations associated with amenorrhea, even in circumstances with a decrease in blood loss due to excess physical exercise.

The patient was a five-year user of the levonorgestrel-releasing intrauterine system when she first reported fatigue symptoms. Clearly, hemochromatosis was not caused by the IUS, but the amenorrhea it promoted may have triggered the symptoms that led to the diagnosis. After her findings, all brothers and sisters were tested and confirmed to be heterozygotes for the same mutation. The family has European ancestry from both parents. Hemochromatosis, the most important iron overload condition of the liver, is the most frequent genetic disease among the Caucasian population, affecting 1 in 300 persons.⁹ An average of 20 mutations have been identified for the HFE gene, the gene responsible for hemochromatosis, but 2 mutations, C282Y and H63D, are the most responsible for abnormal iron loading. The allelic frequencies of C282Y and H63D mutation vary in different populations from under 5% for C282Y to 15% for H63D.¹⁰

In conclusion, it is important to consider the diagnosis of iron overload syndromes in patients with the symptoms described above, but it is particularly important to consider this diagnosis in patients who



wish to suspend menstruation for personal reasons. In these patients, monitoring ferritin levels may be necessary for the diagnosis of an underlying condition that may compromise different systems and have long-term implications.

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Author Contributions

Wrote the first draft of the manuscript: MVM. Contributed to the writing of the manuscript: EVM. Agree with manuscript results and conclusions: MVM, EVM. Jointly developed the structure and arguments for the paper: MVM, EVM. Made critical revisions and approved final version: MVM, EVM. All authors reviewed and approved of the final manuscript.

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References

1. Ravikumara M. Investigation of chronic diarrhoea. *Paediatr Child Health*. 2008;18:441–7.
2. Muscatell KA, Slavich GM, Monroe SM, Gotlib IH. Stressful life events, chronic difficulties and the symptoms of clinical depression. *J Nerv Ment Dis*. 2009;197(3):154–60.
3. Timonen M, Laakso M, Jokelainen J, Rajala U, Meyer-Rochow VB, Keinänen-Kiukaanniemi S. Insulin resistance and depression: cross sectional study. *Br Med J*. 2005;330:17–8.
4. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in US adults. *Diabetes Care*. 1998;21(4):518–24.
5. Liu Q, Sun L, Tan Y, et al. Role of iron deficiency and overload in the pathogenesis of diabetes and diabetic complications. *Curr Med Chem*. 2009;16(1): 113–29.
6. Rana M, Saxena P, Firdous N. Comparison of levonorgestrel and copper releasing intrauterine contraceptive device on body iron stores and menstrual bleeding patterns: experience on Indian women. *Eur Rev Med Pharmacol Sci*. 2012;16:230–4.
7. Faundes A, Alvarez F, Brache V, Tejada AS. The role of the levonorgestrel intrauterine device in the prevention and treatment of iron deficiency anemia during fertility regulation. *Int J Gynaecol Obstet*. 1988;26(3):429–33.
8. Allen K. Hereditary hemochromatosis—diagnosis and management. *Am Fam Physician*. 2010;39(12):938–41.
9. Brissot P, Guyader D, Loréal O, et al. Clinical aspects of hemochromatosis. *Transfus Sci*. 2000;23:193–200.
10. Soria NW, Isasi SC, Chaig MR, Burgos NMG. Analysis of C282Y and H63D mutations of the hemochromatosis gene (HFE) in blood donors from Córdoba, Argentina. *Ann Hematol*. 2009;88:77–9.