Gerontology & Geriatric Medicine
Volume 7: 1–3
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/23337214211067875
journals.sagepub.com/home/ggm
SAGE

Worsening Restless Leg Syndrome Symptoms as a Presentation of Colon Cancer: A Reminder to Work Up the Anemia

Daniel J. Zhou, MD, MS[1,2], Amrita-Amanda D. Vuppala, MD[1], and Swetha Pedavally, MD[1,2]

Abstract

Restless leg syndrome (RLS) is a common neurological disorder with an estimated prevalence of 10–35% in people over 65 years of age. Current clinical practice guidelines include the recommendation to check serum ferritin levels and provide iron supplementation if the ferritin level is ≤75 μg/L. We present a case of an 84-year-old man who developed worsening RLS symptoms over the past year despite up-titration of oral ropinirole to maximum daily dose. As part of his workup for RLS, his serum ferritin level was found to be severely low. He was also previously noted to be anemic, so we recommended that he be worked up for iron deficiency anemia. He later received a colonoscopy, which revealed a cecal polyp with high grade dysplasia, and then underwent right hemicolectomy. The patient reported significant improvement in RLS symptoms following the surgery. This case demonstrates the importance of working up iron deficiency anemia in the setting of worsening RLS symptoms, particularly in the geriatric population.

Keywords

neurology, sleep disorders, cancer

Manuscript received: September 18, 2021; **final revision received:** November 16, 2021; **accepted:** December 2, 2021.

Other Search Terms: restless leg syndrome, iron deficiency, malignancy

Introduction

Restless leg syndrome (RLS) is a common neurologic disorder with an estimated prevalence of 10–35% in people over 65 years of age (Milligan & Chesson, 2002). Restless leg syndrome is characterized by the compelling urge to move the legs, usually due to uncomfortable dysesthesia, worse at night than during the day, and relieved by voluntary movements (Milligan & Chesson, 2002).

The pathophysiology of RLS is complex and remains not fully understood, but it is thought to involve multiple physiologic processes including the dopaminergic and glutaminergic pathways (Manconi et al., 2021). Brain iron deficiency has been implicated in the disease process of RLS, and it is currently theorized that low brain iron levels disrupt striatal dopamine neurotransmission as well as induce hyperglutaminergic and hypoadenosinergic states (Earley et al., 2014; Lanza & Ferri, 2019; Manconi et al., 2021). These changes would then result in dysfunction of the cortical–striatal–thalamic networks and disinhibition of the ascending arousal system, thus giving rise to abnormalities in modulating movements and hyperarousal, respectively (Lanza & Ferri, 2019; Manconi et al., 2021). Clinical trials have demonstrated the efficacy of iron supplementation in patients with RLS who are found to have low ferritin levels, a marker suggestive of low brain iron levels (Davis et al., 2000; Wang et al., 2009).

The current clinical practice guidelines recommend prescribing dopaminergic agents, such as pramipexole, rotigotine,

[1]Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE, USA
[2]Specialty Care-Neurology, VA Nebraska-Western Iowa Health Care System, Omaha, NE, USA

Corresponding Author:
Swetha Pedavally, Department of Neurological Sciences, University of Nebraska Medical Center, 988440 Nebraska Medical Center, Omaha, NE 68198-8440, USA.
Email: swetha.pedavally@unmc.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

cabergoline, or ropinirole (Winkelman et al., 2016). However, augmentation, which is an overall increase in RLS symptom severity, is an important complication of dopaminergic medications that should be monitored (Garcia-Borreguero et al., 2016). Alternative therapies include gabapentin or pregabalin (Winkelman et al., 2016). The guidelines also recommend checking serum ferritin levels and providing iron supplementation (oral ferrous sulfate or intravenous iron) if the ferritin level is ≤75 μg/L (Allen et al., 2018; Winkelman et al., 2016). The following case report additionally highlights the importance of working up iron deficiency anemia in the setting of worsening RLS symptoms, especially in the geriatric population.

Case Report

An 84-year-old man was referred to the Neurology clinic for worsening of RLS symptoms refractory to ropinirole at a total daily dose of 4 mg. He was initially diagnosed with RLS by his primary care provider (PCP) about 4 years prior to his Neurology clinic visit, during which he was started on 0.5 mg ropinirole nightly. Overnight polysomnography was deferred, as the patient fulfilled the clinical criteria for RLS and had significant improvement in symptoms upon taking ropinirole. His RLS remained well controlled until the year prior, when his symptoms progressively worsened and began earlier in the day. His ropinirole was titrated up to 2 mg during the day and 2 mg at night, with only minimal symptomatic benefit.

The patient's past medical history was significant for major depressive disorder on sertraline and prostate cancer (diagnosed at age 65 years). He was a former smoker, with a 40 pack-year history of tobacco use. About 3 months prior to his presentation to the Neurology clinic, he was hospitalized for COVID-19 pneumonia, and his labs at the time were remarkable for normocytic anemia, with hemoglobin (Hb) 8.0 g/dL (normal 12.5–17 for men). His electronic health record showed that his Hb was 12.1 g/dL during the year prior and within normal range during previous lab checks over the past 5 years. Serum iron studies had never been checked.

During his visit in the Neurology clinic, he reported that his legs "had a mind of its own," making it difficult for him to fall asleep at night. Cognitively, he was alert and fully oriented, with intact attention and concentration and impaired delayed recall. Cranial nerves were intact. He frequently walked around the room during the interview, but his neurological examination was otherwise normal. His MRI brain with and without contrast obtained from a year prior was notable for scattered foci of T2 prolongation within the hemispheric white matter, consistent with chronic microvascular disease. Following the visit, iron studies were ordered and revealed serum iron of 15 μg/dL (normal 49–181), ferritin 8 ng/mL (normal 18–464), and normal transferrin levels. He was then started on oral ferrous sulfate 324 mg daily, and his PCP was notified for further evaluation of iron deficiency anemia.

One week later, he presented to his PCP, where upon further questioning, he denied any gastrointestinal or other bleeding, weight change, poor appetite, nausea or vomiting, and constipation or diarrhea. He continued to report severe RLS symptoms at the time. His repeat Hb at the time improved to 11.1 g/dL from 8 g/dL following iron supplementation. He revealed he had never received a colonoscopy for cancer screening and was strongly encouraged to do so. One month later, his colonoscopy revealed a cecal polyp with high grade dysplasia. CT abdomen and pelvis showed no metastatic spread. He subsequently underwent right hemicolectomy without chemotherapy or radiation therapy.

During follow-up with the Neurology clinic 3 months later, the patient reported that his RLS symptoms significantly improved immediately following the surgery and remained well controlled with a total daily dose of 4 mg of ropinirole.

Discussion

In the present case, the patient's ferritin level was found to be severely low, at 8 μg/L. At the time, he denied any symptoms of malignancy, such as gastrointestinal bleeding and unintentional weight loss, likely due to his colon cancer being at an early stage without any metastases. Nevertheless, we suspect that the tumor was likely a major contributor to the loss of iron stores in the blood, resulting in the exacerbation of his RLS symptoms. This was supported by the fact that he continued to report severe RLS symptoms despite iron supplementation and maximum therapeutic dosing of ropinirole until after undergoing surgical resection at the region of the tumor.

The cause of RLS is currently thought to be due to a combination of genetic and environmental factors, as an association has been established between RLS and a positive family history, iron deficiency, and kidney disease (Trenkwalder et al., 2016). The possible association between RLS and cancer continues to be explored. There have been a few case reports of RLS as an early symptom of malignancy, including multiple myeloma, bladder cancer, and gastrointestinal cancer (Brocklehurst, 2003; EKBOM, 1955; Parish, 2005). On a larger scale, an epidemiological study in Europe found a significantly increased prevalence of cancer in patients with RLS compared to the age-matched general population (Fuhs et al., 2014). Likewise, a large cross-sectional study also reported the prevalence of RLS in cancer patients undergoing chemotherapy in Italy to be 18.3%, nearly twice greater than that of the general population (Ostacoli et al., 2010). Given our current understanding of the pathophysiology of RLS, we suspect that the increased prevalence of RLS in the setting of cancer is likely associated with the inherent disruption of brain iron homeostasis present in cancer, especially in our case of the patient with colon cancer, who was found to be severely deficient in ferritin in the blood.

Although it should be intuitive, the current recommendations for management of RLS do not directly mention the need to work up the cause of iron deficiency anemia, but they do report the expectation of improved symptoms with correction of the anemia (Allen et al., 2018; Garcia-Borreguero et al., 2016). The workup of iron deficiency anemia becomes especially important in the geriatric population, who

inherently have a higher risk of developing cancer. Although we did not find published data on how often this workup is overlooked in the setting of RLS, we have observed multiple cases of this from our own clinical experience. In the setting of worsening symptoms of RLS, this case provides an example of why it is so important to not only provide iron supplementation when ferritin levels are low, but also address and correct the underlying cause of iron deficiency.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Patient Consent

The authors have obtained written informed consent from the patient, which is available for verification upon request.

ORCID iD

Daniel J. Zhou https://orcid.org/0000-0002-0154-8348

References

Allen, R. P., Picchietti, D. L., Auerbach, M., Cho, Y. W., Connor, J. R., Earley, C. J., Garcia-Borreguero, D., Kotagal, S., Manconi, M., Ondo, W., Ulfberg, J., & Winkelman, J. W. (2018). International Restless Legs Syndrome Study Group (IRLSSG)Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/willis-ekbom disease in adults and children: An IRLSSG task force report. *Sleep Medicine*, *41*, 27-44. https://doi.org/10.1016/j.sleep.2017.11.1126.

Brocklehurst, J. (2003). Restless legs syndrome as a presenting symptom in malignant disease. *Age and Ageing*, *32*(2), 234. https://doi.org/10.1093/ageing/32.2.234.

Davis, B. J., Rajput, A., Rajput, M. L., Aul, E. A., & Eichhorn, G. R. (2000). A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. *European Neurology*, *43*(2), 708138–708145. https://doi.org/10.1159/000008138.

Earley, C. J., Connor, J., Garcia-Borreguero, D., Jenner, P., Winkelman, J., Zee, P. C., & Allen, R. (2014). Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (willis-ekbom disease). *Sleep Medicine*, *15*(11), 1288–1301. https://doi.org/10.1016/j.sleep.2014.05.009.

EKBOM, K. A. (1955). Restless legs as an early symptom of cancer. *Svenska Lakartidningen*, *52*(30), 1875-1883.

Fuhs, A., Bentama, D., Hoffmann, W., Völzke, H., Mathis, J., Kraywinkel, K., & Berger, K. (2014). (Invalid date). Restless legs syndrome and cancer: An analysis in three independent studies. *Epidemiology Reports*, *2*(1), 4. https://doi.org/10.7243/2054-9911-2-4.

Garcia-Borreguero, D., Silber, M. H., Winkelman, J. W., Högl, B., Bainbridge, J., Buchfuhrer, M., Hadjigeorgiou, G., Inoue, Y., Manconi, M., Oertel, W., Ondo, W., Winkelmann, J., & Allen, R. P. (2016). Guidelines for the first-line treatment of restless legs syndrome/willis-ekbom disease, prevention and treatment of dopaminergic augmentation: A combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Medicine*, *21*, 1-11. https://doi.org/10.1016/j.sleep.2016.01.017.

Lanza, G., & Ferri, R. (2019). The neurophysiology of hyperarousal in restless legs syndrome: Hints for a role of glutamate/GABA. *Advances in Pharmacology (San Diego, Calif.)*, *84*, 101-119. https://doi.org/10.1016/bs.apha.2018.12.002.

Manconi, M., Garcia-Borreguero, D., Schormair, B., Videnovic, A., Berger, K., Ferri, R., & Dauvilliers, Y. (2021). Restless legs syndrome. *Nature Reviews.Disease Primers*, *7*(1), 80–021. https://doi.org/10.1038/s41572-021-00311-z.

Milligan, S. A., & Chesson, A. L. (2002). Restless legs syndrome in the older adult: Diagnosis and management. *Drugs & Aging*, *19*(10), 741–751. https://doi.org/10.2165/00002512-200219100-00003.

Ostacoli, L., Saini, A., Ferini-Strambi, L., Castronovo, V., Sguazzotti, E., Picci, R. L., Toje, M., Gorzegno, G., Capogna, S., Dongiovanni, V., Dogliotti, L., Furlan, P. M., & Berruti, A. (2010). Restless legs syndrome and its relationship with anxiety, depression, and quality of life in cancer patients undergoing chemotherapy. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *19*(4), 531–537. https://doi.org/10.1007/s11136-010-9614-8.

Parish, J. M. (2005). I can't sleep at night" an unusual case of insomnia. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, *1*(3), 305–308. https://doi.org/10.5664/jcsm.26348.

Trenkwalder, C., Allen, R., Högl, B., Paulus, W., & Winkelmann, J. (2016). Restless legs syndrome associated with major diseases: A systematic review and new concept. *Neurology*, *86*(14), 1336–1343. https://doi.org/10.1212/WNL.0000000000002542.

Wang, J., O'Reilly, B., Venkataraman, R., Mysliwiec, V., & Mysliwiec, A. (2009). Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. *Sleep Medicine*, *10*(9), 973–975. https://doi.org/10.1016/j.sleep.2008.11.003.

Winkelman, J. W., Armstrong, M. J., Allen, R. P., Chaudhuri, K. R., Ondo, W., Trenkwalder, C., Zee, P. C., Gronseth, G. S., Gloss, D., & Zesiewicz, T. (2016). Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. *Neurology*, *87*(24), 2585–2593. https://doi.org/10.1212/WNL.0000000000003388.