

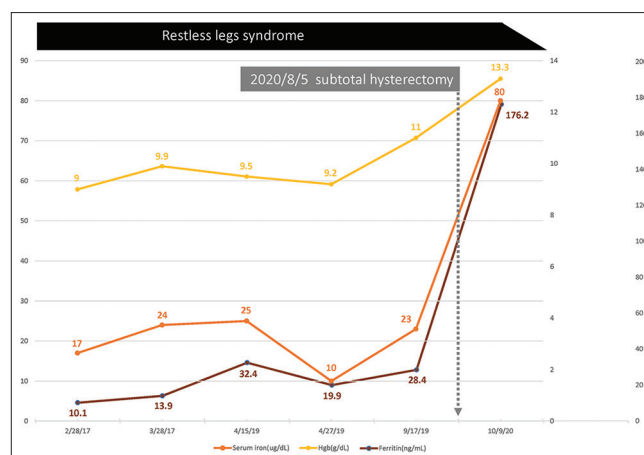
## Refractory Restless Legs Syndrome Secondary to Combined Folate Deficiency and Iron-Deficiency Anemia in a Young Female with Major Depressive Disorder: A Case Report

Dear Editor,

Recent studies have indicated that restless legs syndrome (RLS) is common among psychiatric patients compared to the general population.<sup>1</sup> Additionally, the prevalence of RLS is significantly higher in females compared to males, being twice as common in women, and particularly prevalent during pregnancy.<sup>2</sup> Current etiological hypotheses suggest that RLS is a complex disorder with heterogeneous genetic determinants and significant contributions from iron deficiency and dysregulation of the dopaminergic system.<sup>2</sup> Herein, we present the case of a female patient with major depressive disorder who was subsequently diagnosed with RLS. Further evaluation revealed that her RLS was associated with both folate and iron deficiencies.

A 36-year-old Taiwanese woman was admitted to the psychiatric ward for a major depressive episode. She was prescribed escitalopram at 10 mg/day to manage her depressive symptoms. The patient had no significant medical history or history of substance abuse, except for iron-deficiency anemia secondary to heavy menstrual bleeding over the past few years. During her hospitalization, she experienced an electric sensation within the legs, along with an uncomfortable urge to move her legs, particularly at night, with symptoms worsening after episodes of heavy menstrual bleeding. A neurological examination showed no abnormalities in the central or peripheral nervous system, leading to a diagnosis of RLS after consulting a neurologist. Laboratory tests revealed low serum iron level (17 µg/dL), low ferritin level (10.1 ng/mL), low hemoglobin level (9.0 g/dL), and low mean corpuscular volume (63.8 fL). The patient was started on oral iron supplementation (100 mg/day), along with the dopamine agonist ropinirole (2 mg/day), and clonazepam (3 mg/day). Additionally, a short trial of pregabalin was also administered but was discontinued due to significant dizziness at low doses. However, her RLS did not fully remit.

At her age of 39 years, she underwent a subtotal hysterectomy for menorrhagia-induced iron-deficiency anemia. Despite the normalization of hemoglobin (13.3 g/dL), serum iron level (105 µg/dL), and ferritin level (176.2 ng/mL) postsurgery, her leg movements persisted [Figure 1]. A subsequent nerve conduction velocity study revealed mild peroneal axonopathy. Further investigation revealed the patient followed a predominantly carnivorous diet. Laboratory evaluation showed a low serum folate level (1.1 ng/mL). After initiating folate supplementation (2.5 mg/day), her serum folate level



**Figure 1:** The association between restless legs syndrome and changes in serum iron, hemoglobin, and ferritin levels before and after subtotal hysterectomy

normalized (21.3 ng/mL), and the leg movements completely subsided within 2 weeks. When folate supplementation was discontinued, the RLS symptoms recurred. This led to the final diagnosis of RLS attributed to both folate and iron deficiencies.

RLS is a prevalent sleep-related movement disorder characterized by an uncomfortable urge to move the legs, especially during periods of inactivity, typically in the evenings. Peripheral neuropathy may mimic RLS, but it typically does not exhibit worsening symptoms at night. Although this case presents with mild peroneal axonopathy, numerous studies have suggested that RLS itself may be associated with mild peripheral neuropathy.<sup>3</sup> Despite its prevalence, the pathogenesis of RLS remains somewhat uncertain. In this case, RLS was associated with not only chronic iron-deficiency anemia but also dietary habits-related folate deficiency. Both iron and folate deficiency are proposed contributors to RLS. A reduction in tyrosine hydroxylase, an iron-dependent enzyme crucial for dopamine synthesis, had been implicated in iron deficiency-induced RLS. Similarly, folate, in the form of 5-methyltetrahydrofolate, enhances the production of central nervous system tetrahydrobiopterin, a cofactor essential for tyrosine hydroxylase synthesis, and plays a critical role in neurotransmitter production within the brain's dopaminergic system.<sup>4,5</sup> Besides, stress from the subtotal hysterectomy may have also temporarily exacerbated the symptoms of RLS and contributed to the delayed response despite the normalization of iron levels.<sup>6</sup>

Several studies have shown that the prevalence of RLS is significantly higher among patients with mental illness, particularly in those with depressive or anxiety disorders.<sup>1</sup> Persistent RLS may exacerbate their mental conditions through sleep disturbances when underscoring the importance of assessing RLS symptoms during psychiatric evaluations. Moreover, the use of certain antidepressants may worsen RLS symptoms.<sup>7</sup> Stopping or shifting to other antidepressants had been done during past years, the RLS did not remit in this patient excluding the causal relationship between antidepressants and RLS symptoms. Failure to diagnose or treat RLS can contribute to increased psychological stress and worsen the burden of psychiatric illness.<sup>8</sup>

Among women of reproductive age and those with comorbid psychiatric conditions who have RLS, it is essential to take a detailed history to assess whether symptoms correlate with the menstrual cycle or specific dietary habits. Additionally, laboratory tests for iron, ferritin, and folate levels are recommended to identify potential deficiencies that may contribute to RLS.

### Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In this form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Y. C. Huang and Y. W. Yeh conceived the concept of this article. C. Y. Chen provided the clinical insights in this case. H. Fang wrote the first draft and was edited by Y. C. Huang (hollykid11415@mail.ndmctsgh.edu.tw) and Y. W. Yeh (ywyeh@mail.ndmctsgh.edu.tw) contributed in conducting the critical revision of the article and served as the corresponding authors. All authors approved this manuscript.

### Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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