Restless Legs Syndrome: Pathophysiology and the Role of Iron and Folate

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Abstract

Restless Legs Syndrome (RLS) is a common movement disorder characterized by a circadian variation in symptoms involving an urge to move the limbs, usually the legs. Pregnant women, patients with end-stage renal disease or iron-deficiency anemia, and children with attention deficit hyperactivity disorder (AD/HD) have a significantly higher prevalence of RLS. The classic presentation includes the onset or worsening of symptoms when at rest and the circadian pattern of exacerbation of symptoms at night. These symptoms reflect a circadian fluctuation of dopamine in the substantia nigra. Patients with RLS have lower levels of dopamine in the substantia nigra and respond to iron administration. Iron, as a cofactor in dopamine production, plays a central role in the etiology of RLS. Folic acid administration has also been shown to alleviate the symptoms of RLS and may play a role in the treatment of primary (familial) RLS. *(Altern Med Rev* 2007;12(2):101-112)

Introduction

Restless Legs Syndrome (RLS) is a neurological movement disorder that is common, under-diagnosed, under-treated, and has a poorly understood etiology.[1] Due to a lack of awareness among primary care providers, both misdiagnosis and mistreatment of RLS appear to be common.[2] Studies in North America and Northern Europe confirm RLS is a common disorder with a prevalence of 5-25 percent in the general population.[3-8] It is twice as prevalent in women,[9] and more common in the elderly, with 10-20 percent over age 65 experiencing significant symptomology.[10]

A study of 23,052 primary care patients evaluated for RLS revealed that nine percent had weekly symptoms of RLS. Although the majority of those diagnosed (88%) had primary complaints of insomnia, only 13 percent had actually received a prior diagnosis of RLS.[2] Of those who had received a prior diagnosis, the majority had been prescribed therapies known to be ineffective in RLS. Misdiagnoses included varicose veins, other venous disorders, depression, myalgia, back or spinal injury, and diabetic neuropathy.

Diagnostic Criteria

RLS is classified as either familial (primary RLS), with a clear genetic component, or acquired (secondary RLS). Primary RLS occurs in approximately 50 percent of first-degree relatives of those with RLS and is believed to be related to an inherited defect in dopamine metabolism.[11] Acquired RLS involves altered iron metabolism and occurs in a variety of patient populations, including pregnant women, patients with end-stage renal disease, and individuals with iron deficiency.[12]

The diagnosis of RLS consists of four essential clinical criteria based solely on symptoms (Table 1).[13] A compelling urge to move the limbs occurs on resting or lying down and discomfort is alleviated by movement of a body part (usually the legs) or the entire body. RLS is also characterized by involuntary or spontaneous movement, such as floor pacing, tossing and turning in bed, and rubbing the legs to relieve sensations – described

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as "creeping, crawling, itching, burning, searing, tugging, drawing, aching, like an electric current."[1] The symptoms have a circadian pattern – always improved when at rest in the morning and worse when at rest in the evening.[13]

Table 1. Essential Clinical Criteria for Diagnosis of RLS

1.	A sensation of an urge to move the limbs (commonly legs) – usually associated with paresthesia
2.	Onset or worsening of symptoms when at rest – not associated with any specific body position.
3.	Relief of symptoms with movement; complete relief immediately or shortly after initiating movement.
4.	Marked circadian variation in degree or occurrence of symptoms; worse in the evening, improved in the morning regardless of quality or quantity of sleep.

Differential Diagnosis

Several other disorders resemble RLS and are differentiated by symptom description, laboratory testing, and other appropriate diagnostic workup (Table 2).[14] Neuropathies and radiculopathies can be ruled in or out by electrophysiological assessment and testing blood levels of glucose (fasting), thyroid hormone, vitamin B6, and vitamin B12.[15] Abnormalities of any of these would help rule out RLS.

Table 2. Differential Diagnosis – to Differentiate from RLS

Peripheral Neuropathy	No circadian changes No periodic leg movements in sleep Nerve conduction abnormal No improvement with movement
Akathisia	No circadian pattern No paresthesia Improvement from dopamine blockers
Peripheral Vascular Disease	Worse with movement, better with rest Vascular and skin changes seen on exam
Nocturnal Leg Cramps	Unilateral, focal, sudden severe onset
Painful Legs and Moving Toes	No urge to move, no worsening at rest or improvement with movement No circadian changes

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Table 3. Populations At-Risk for Restless Legs Syndrome

Pregnancy
End-stage renal disease on hemodialysis
Primary family history of RLS
Iron deficiency anemia
Frequent blood donations
Gastric surgery
Pediatric AD/HD

RLS: A Cause of Serious Sleep Impairment

RLS is a form of sleep disorder that includes periodic limb movements in sleep (PLMS), a condition where involuntary motor movements of the limbs occur during the sleep cycle and lead to a shift in sleep stage and repeated awakenings.[12] PLMS can also occur in conditions such as narcolepsy, Parkinson's disease, and other disorders related to impairments in dopamine production.[16] PLMS is more prevalent as age increases – up to 30 percent of individuals over age 50 experience PLMS secondary to a disease state or medication side effect.[17]

Approximately 20 percent of those with RLS do not have involuntary motor movements during sleep (it is not necessary for a diagnosis). However, the condition results in severe sleep disruption for the majority of RLS patients and has been recognized as a cause of sleep impairment in 5-10 percent of the U.S. population.[18] Because PLMS leads to multiple awakenings at night, RLS is considered the fourth-leading cause of insomnia. Sleep impairment, although usually not voluntarily disclosed without direct questioning, is the main complaint described by those with RLS.[19] RLS results in sleep impairment equal to or greater than any other sleep disorder. In one polysomnographic study of 26 RLS patients, sleep efficiency was decreased by 50 percent, leaving 30 percent of patients with less than 3.5 full hours of sleep nightly.[12] With the exception of mania, severe RLS results in the greatest level of sleep deprivation of any sleep disorder.[12]

Given recent findings that show 30-40 percent of those with chronic insomnia may also have clinical depression, this level of sleep deprivation may be related to the significantly higher incidence of anxiety and depression in RLS patients compared to the general population.[18] Patients presenting in a sleep disorder clinic with either RLS or periodic leg movement disorder (PLMD) had a greater than 50 percent chance of having some form of depression.[20] The negative impact of RLS on quality of life has been shown to be equal to or greater than chronic obstructive pulmonary disease or myocardial infarction.[12]

At-Risk Populations for RLS

Pregnancy, end-stage renal disease, certain medications, and iron deficiency are associated with a significantly higher incidence of RLS (Table 3).[15]

Pregnancy

During pregnancy the incidence of iron deficiency is significant; less than optimal iron intake can occur in 90 percent of pregnant American women.[21] Research estimates 11-27 percent of pregnant women experience RLS at some point during pregnancy, most commonly in the third trimester.[22-24] RLS is the most common movement disorder in pregnancy and generally remits with delivery.[25]

The etiology of RLS in pregnancy is related to iron and folate insufficiency. During normal pregnancy, the requirements for both nutrients increase significantly – iron requirement increases 3- to 4-fold and folate requirement increases 8- to 10-fold.[22] Deficiencies of either nutrient have been found in pregnant women with RLS, and the resolution of RLS appears to correlate with normalization of folate and iron levels postpartum.[26] The prevalence of RLS in women receiving folate supplementation throughout pregnancy was significantly lower compared to the prevalence in women with no folate supplementation (9% versus 80%, respectively).[27]

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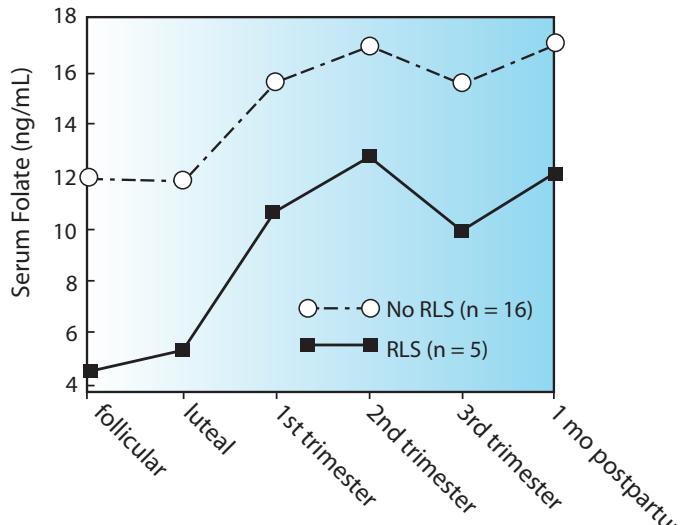
In a prospective trial of pregnant women with RLS and matched pregnant controls, hemoglobin and serum folate, iron, ferritin (storage iron), and vitamin B12 were monitored preconception and once each trimester.[26] Although no serum folate measurements fell below the normal range of 4-20 ng/mL, folate levels were significantly lower in the RLS group (Figure 1) prior to conception and during the ensuing nine months. Although not statistically significant, serum ferritin levels were also consistently lower in the RLS group. Hemoglobin and serum iron and vitamin B12 were similar in both groups. The study design was weak because it used a single indicator of the symptom of restless legs at the onset of sleep or being awakened by leg cramps, instead of the four clinical criteria outlined in Table 1. However, consistently significant differences in folate levels throughout the three-trimester study period do point to a relationship between serum folate and RLS symptoms. Serum ferritin levels in those with RLS were consistently below 50 ng/mL (Figure 2) and indicate increased risk for an iron metabolism-related etiology for RLS in these women.

Figure 1. Changes in Serum Folate from Preconception until One-month Postpartum



From: Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gend Based Med* 2001;10:335-341. Used with permission.

End-stage Renal Disease

Another group at risk for RLS are individuals on hemodialysis with end-stage renal disease (ESRD). A recent survey found as much as 62 percent of ESRD patients complain of RLS symptoms,[28] while the actual prevalence in another group of ESRD patients using the 1995 criteria (Table 1) was 21 percent.[29] The presence of RLS symptoms can predict increased mortality in these patients. Even though a kidney transplant, which resolves the renal disease, leads to a disappearance of all RLS symptoms within three weeks, it does not decrease the mortality risk.[30] Although there does not seem to be a correlation between RLS and degree of uremia or parathormone levels in ESRD patients, the rate of occurrence is directly related to duration of dialysis.[29]

Evidence for a possible relationship of iron deficiency to RLS in this patient population has been explained by the universal occurrence of anemia, which is commonly acquired in patients with end-stage renal disease due to inadequate production of erythropoietin.[31,32] Anemia in ESRD is associated with several co-morbid conditions, including congestive heart failure, stroke, cognitive dysfunction, left ventricular hypertrophy, and worsening iron deficiency due to loss from hemodialysis.[29] Ferritin levels under 100 ng/mL reflect depletion of iron stores and complicate the treatment of anemia in patients on dialysis.[33] Treatment of ESRD-associated anemia with erythropoietin has been shown to decrease arousal due to PLMS and produce trends toward higher sleep quality.[34] As will be reviewed later, intravenous (I.V.) iron in ESRD patients has been shown to be highly effective in causing remission of RLS symptoms.[35]

Lifestyle Factors and Medications Affecting RLS

Lifestyle factors and certain medications, particularly those with antidopaminergic effects, can also initiate or exacerbate RLS (Table 4).[15] Medications that can induce or exacerbate RLS include selective serotonin reuptake inhibitors (SSRIs),[36] lithium,[37] dopamine agonists, tricyclic antidepressants, antiemetics, antipsychotics, and any medication with antidopaminergic activity.[15]

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Figure 2. Changes in Serum Ferritin from Preconception to One-month Postpartum

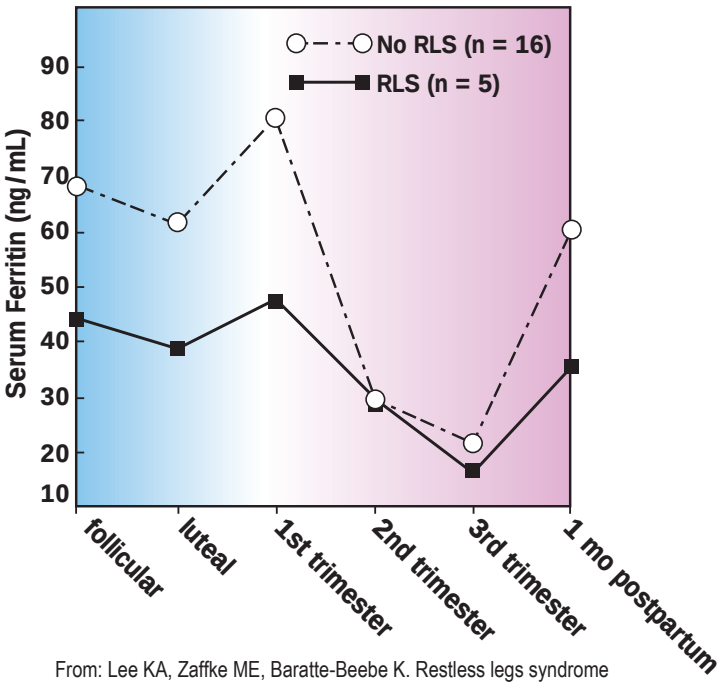

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Table 4. Medications and Lifestyle Factors that Trigger or Exacerbate RLS

Lifestyle Factors
Caffeine
Nicotine
Alcohol
Medications
SSRIs
Tricyclic antidepressants
Metoclopramide
Prochlorperazine maleate
Dopamine antagonists
Diphenhydramine

Nutrient Deficiencies Associated with RLS

Iron

Populations at increased risk for iron insufficiency are also at increased risk for RLS, including gastric bypass surgery patients,[38] frequent blood donors,[39] and the elderly.[40]

Children with AD/HD are at risk for iron insufficiency and an increased incidence of PLMS and RLS.[41] A study involving 886 pediatric patients (ages 2-14 years) found that symptoms of PLMS occurred more commonly in children with high hyperactivity scores, even when controlling for stimulant use.[42]

Like pregnant women and patients with end-stage renal disease, children with AD/HD are also more likely to have low serum ferritin levels. In one study that did not assess RLS symptoms but did look at iron storage capacity, ferritin values in children with AD/HD were almost 50-percent lower (23±13 ng/mL) than controls (44±22 ng/mL).[43] Another study of 68 children attending an AD/HD clinic, however, found serum ferritin levels were not significantly different than controls.[44] Other trials have confirmed iron insufficiency in a large percentage of AD/HD children. Iron insufficiency (interpreted by serum ferritin <30 ng/mL) was seen in 84 percent of children with AD/HD compared to 18 percent of controls. Treatment of low ferritin levels in young males with AD/HD (iron [as citrate] 5 mg/kg/day for 30 days) resulted in a significant rise in ferritin levels and a significant decrease in attention deficit/hyperactivity rating scores by parents.[45]

Iron levels in the brain have been shown to influence dopamine metabolism and dopaminergic agonists have been shown to successfully treat RLS symptoms.[46] One small trial examining the effect of dopaminergic agents in pediatric AD/HD and RLS yielded good results.[46] Of the seven children in the trial given either levodopa or pergolide, all responded with significant reduction in RLS symptoms and decreased leg movements during sleep (p=0.018). With the exception of this one trial, there is only limited information from case reports of significant symptom reduction in pediatric RLS using dopaminergic agents.[46,47]

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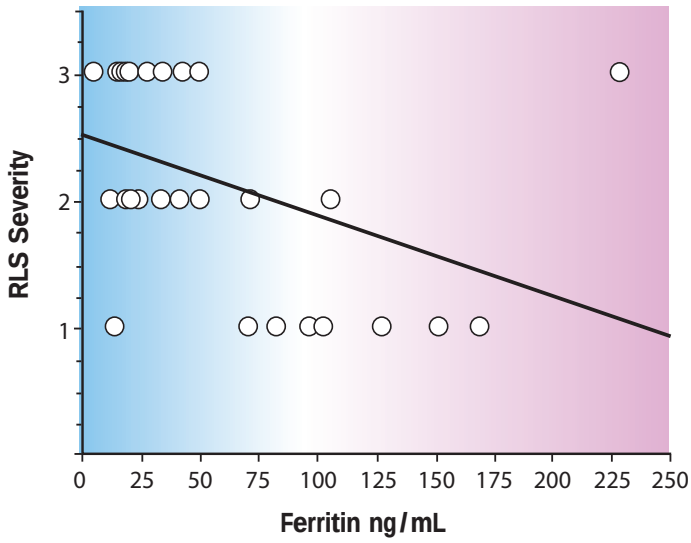
Iron Metabolism and RLS

Studies of RLS and iron metabolism have revealed a key role for low brain iron concentrations in altered dopamine levels.[48] An assessment of individuals in all groups with a high incidence of iron deficiency – pregnancy, end-stage renal disease, anemia – found a 25- to 30-percent incidence of RLS.[12] Conversely, in one study 75 percent of individuals with RLS symptoms demonstrated decreased iron stores.[49] Another retrospective study found that, although 62.5 percent of RLS patients had low serum iron and 77 percent had low iron saturation, only 21 percent had red blood cell (RBC) indices of anemia and only 25 percent had low ferritin levels.[50] Significant decline in serum ferritin (32.5 ng/mL in RLS versus 59 ng/mL in controls) has been seen in elderly patients with RLS.[38]

Although ferritin levels in RLS are often "low normal" (i.e., above the lab reference range low of 20 ng/mL), a specific threshold of inadequate iron storage has been identified as the determining factor in these patients. Ferritin concentrations of <50 ng/mL have been correlated with decreased sleep efficiency, increased leg movements in sleep, and increased symptom severity (insomnia and paresthesias) (Figure 3).[49]

Figure 3. RLS Severity and Serum Ferritin Levels



Adapted from: Sun ER, Chen CA, Ho G, et al. Iron and the restless legs syndrome. *Sleep* 1998;21:371-377. Used with permission.

Iron concentrations in the blood have a circadian rhythm, exhibiting a 50- to 60-percent lower serum level at night compared to daytime levels.[51,52] The lowest point in serum iron levels has been found to coincide with the maximal severity of RLS symptoms and is thought to be responsible for the worsening of RLS symptoms in the evening.[53] This diurnal variation of serum iron is also reflected in central nervous system (CNS) iron storage. One study found that nighttime levels of ferritin in cerebrospinal fluid (CSF) were significantly lower in RLS, particularly in early-onset RLS (before age 45).[54]

Even when levels of serum iron, serum ferritin, or serum transferrin (the glycoprotein that binds to and transfers iron from the gut or storage sites to distant sites in the body or within the CNS) are not lower than normals, CSF levels of storage iron have been shown to be significantly lower in RLS. CSF ferritin was 65-percent lower and CSF transferrin was 300-percent higher in patients with RLS compared to age-matched controls.[55,56] Elevation of CSF transferrin is compensatory for low CNS iron levels. The substantia nigra, a "movement center" of the brain and the focal area of pathology in RLS, appears to have both decreased iron uptake and decreased iron storage activity in RLS. MRI measurements of brain iron in five RLS subjects showed significantly less iron in the substantia nigra compared to controls,[57] with decreased levels proportionate to the severity of RLS symptoms. Brain biopsies from seven RLS subjects have also shown decreased iron in the substantia nigra.[58]

The etiopathology of RLS may involve iron storage in certain brain centers. The substantia nigra, along with the putamen and other basal ganglia nuclei, do not have the capacity to store iron as ferritin, but instead rely on a weaker iron-containing pigment known as neuromelanin. Although the function of neuromelanin is not well understood, it may possibly contribute to the sensitivity of the substantia nigra to altered iron metabolism and decreased dopamine availability.[59]

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Iron Replacement in RLS

Serum ferritin of less than 50 ng/mL or iron saturation of less than 16 percent is diagnostic for iron-deficiency associated RLS.[60] Iron replacement in RLS has not been shown to be effective when ferritin levels are above 50 ng/mL.[61] Although there is no standard treatment for iron deficiency in RLS, a suggested protocol includes 50-65 mg elemental iron with 200 mg vitamin C on an empty stomach 1-3 times daily, depending on the degree of deficiency.[15] The goal is to reach a serum ferritin level of 60 ng/mL, with iron studies repeated every three months. To avoid worsening of an undiagnosed hemochromatosis, transferrin saturation levels should not rise over 45 percent.

Low- and high-dose I.V. iron have been used in multiple studies to successfully improve symptoms of both primary and secondary RLS.[48,62] Like with oral iron supplementation, the goal with I.V. iron therapy is to achieve a serum ferritin level of 60 ng/mL, with each infusion of 100 mg iron raising ferritin approximately 10 ng/mL.[15] Because anaphylaxis has been reported with the use of iron dextran, a newer formulation of iron-sodium ferric gluconate complex, which has not had such negative reportage, has been investigated and is considered safer. I.V. iron therapy affords short-term symptom improvement lasting an average of 5-6 months followed by a return of previous symptoms.[48]

Oral dosing iron studies with RLS are limited. In a small case series, three adolescents with RLS and severe insomnia were given 300 mg ferrous sulfate (59 mg elemental iron) either two or three times daily for 4-5 months.[63] Serum ferritin levels at the beginning of treatment were 22, 3, and 26 ng/mL in the three patients. After 4-5 months of treatment, ferritin levels were 35, 14, and 36 ng/mL. Mean sleep latency (time from getting into bed until falling asleep) improved from 143 to 23 minutes, and sleep efficiency (time spent in uninterrupted sleep) improved from 75.7 percent to 84 percent. An oral dosing study in 17 elderly patients with RLS compared ferritin levels with controls and involved intervention in those with RLS and a serum ferritin level below 100 ng/mL – a less conservative level than suggested in other literature.[38] A dose of 200 mg ferrous sulfate three times daily for 8-20 weeks resulted in a rise of baseline serum ferritin values by 10-69 ng/mL. Significant symptom improvement (restless feeling in legs), evaluated by symptom scoring, was observed in all subjects, even those with an initial serum ferritin of 45-100 ng/mL.

Data on I.V. iron in RLS clearly shows a more rapid increase in serum ferritin levels and a more effective resolution of symptoms than oral iron supplementation.[48] It is not clear, however, whether I.V. iron has long-term benefit. One study comparing I.V. versus oral iron therapy in postpartum anemia found no significant difference in hemoglobin measurements between women treated with I.V. ferrous sucrose (200 mg single dose) and oral ferrous sulfate (200 mg twice daily for 40 days).[64] Because standard ferrous iron preparations (ferrous sulfate, ferrous gluconate) are associated with a high incidence of gastrointestinal side effects and poor absorption relative to amino acid chelate forms of iron, compliance is poor and treatment often ineffective.[65] There have been no studies in RLS with newer forms of iron that have superior availability and decreased side effects, such as bis-glycino iron, ferric trimaltol,[66,67] iron citrate, iron picolinate, or iron fumarate.

Folate and RLS

A small cohort of patients with restless legs and paraesthesias has reported improvement with folic acid therapy.[68,69] The first two groups of seven total patients acquired folate deficiencies due to jejunal atrophy or a nutritionally deficient diet. In addition to RLS symptoms, these patients experienced depression, fatigue, depressed Achilles tendon reflex, and lower limb numbness and tingling.[68] A third group of nine patients with idiopathic folate deficiency experienced neurological signs and symptoms identical to the first two groups. Lab indices in these patients did not universally reflect folate deficiency. For example, there was no evidence of megaloblastosis (increased RBC size) in five patients, RBC folate levels were normal in all patients, and only 12 patients had low serum folate concentrations. However, five patients had low CSF folate concentrations and 11 patients had abnormal CT scans reflecting cerebral atrophy. Folate supplementation improved all symptoms in all patients, even in the patients with normal RBC folate levels. Initially, symptoms improved with vitamin B12 administration used for a Schillings test, but did not resolve until patients received daily doses of 1-10 mg folic acid. In addition, I.Q. levels significantly improved after 6-12 months of folate supplementation.[69]

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Additional research involved five families of 45 individuals with familial (primary) folate-responsive RLS.[70] Daily folic acid requirements for these individuals varied between 5 and 30 mg and were determined by the dosage necessary to restore serum folic acid to normal levels (10-12 ng/mL). With any reduction of dosage the symptoms reappeared within 2-7 weeks. The author commented that the absence of megaloblastosis or low RBC folate does not rule out a folic acid insufficiency in patients with neurological disorders, including RLS.

The evidence for low folate in pregnancy-related restless legs syndrome has been reviewed above (see Pregnancy).

The Role of Iron and Folate in Dopamine Metabolism

Several factors support the hypothesis that alterations in dopamine metabolism form the central pathology of RLS.[71] First, medications that increase dopamine activity have been found to effectively reduce RLS symptoms.[72-75] Dopaminergic agents are considered the pharmacological treatment of choice for primary RLS; whereas, in secondary RLS (pregnancy, end-stage renal disease, anemia) iron replacement is the treatment of choice if serum ferritin is below 50 ng/mL and transferrin saturation is less than 50 percent.[24] Pharmaceuticals currently used to treat RLS, with the exception of gabapentin that is indicated for RLS with neuropathy, are all dopaminergic agents (e.g., pergolide, ropinirole, pramipexole, and cabergoline).[76] Augmentation, referring to exacerbation of RLS (earlier onset, increased severity, shorter periods of relief from symptoms), occurs in 50-85 percent of patients on long-term treatment with levodopa. Thus, the dopamine agonists with longer half-lives and decreased risks for augmentation are preferred.[77] Augmentation may still occur in the preferred dopamine agonists, however, and side effects (fatigue, nausea, peripheral edema, dizziness) occurred in 57 percent of patients taking the drug (pramipexole, ropinirole, or pergolide) for at least six months.[78]

Further evidence for the involvement of faulty dopamine metabolism in RLS is that dopamine antagonists, such as metoclopramide (Reglan®) and pimozide (Orap®), can exacerbate RLS symptoms.[79,80] In addition, dosages of pain medications used in RLS (e.g., opioids, gabapentin) are used at significantly high levels that indicate an indirect non-specific effect and do not appear to directly alter dopamine pathways. In other words, if RLS is related to GABA or opiate metabolism defects, smaller doses of either medication should bring relief.[71]

Figure 4. Tyrosine to Dopamine using Tyrosine Hydroxylase as a Rate-limiting Enzyme

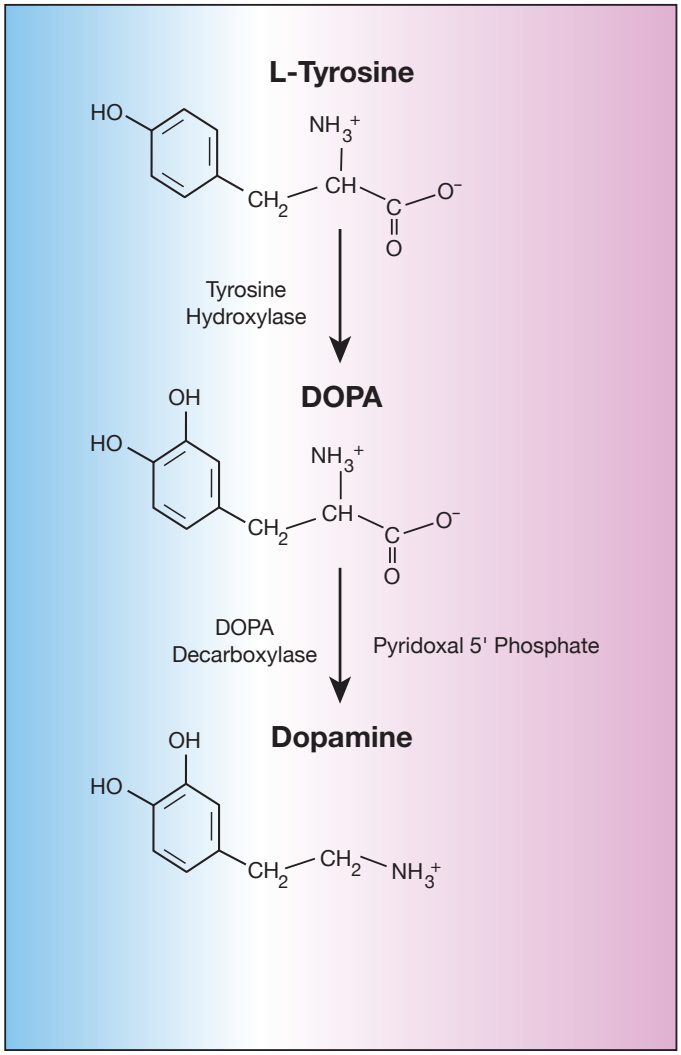

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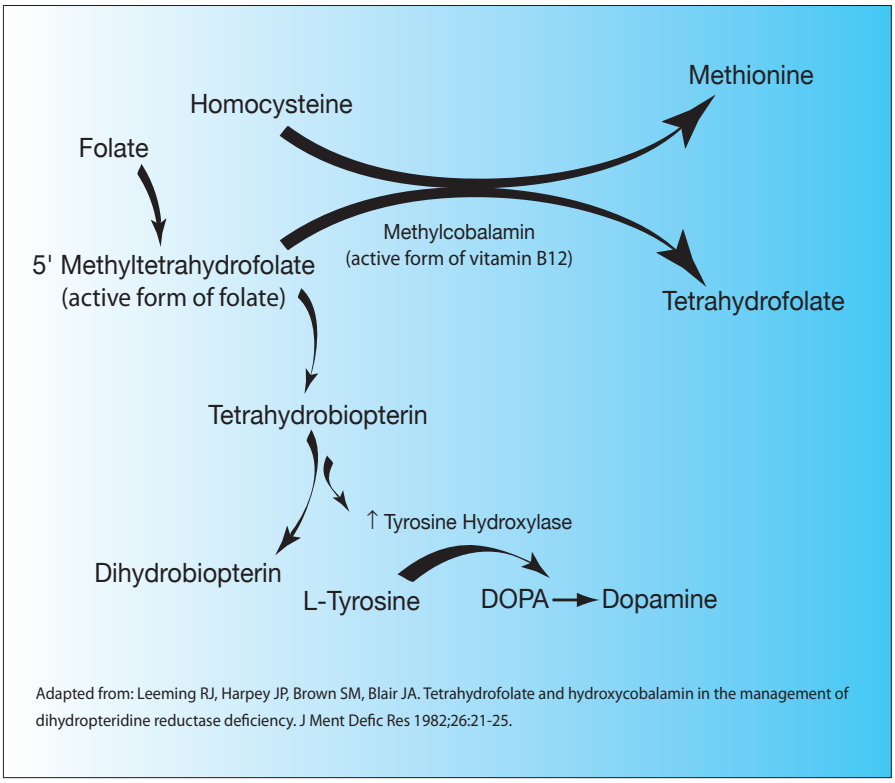
Figure 5. Folate Increases Tetrahydrobiopterin Availability and Furthers Dopamine Production



Adapted from: Leeming RJ, Harpey JP, Brown SM, Blair JA. Tetrahydrofolate and hydroxycobalamin in the management of dihydropteridine reductase deficiency. J Ment Defic Res 1982;26:21-25.

A distinct characteristic of mild-to-moderate RLS – exacerbation of symptoms at night – appears to be consistent with circadian variations in elements of dopamine function. Dopamine metabolism has a circadian rhythm in humans characterized by an increased level of activity in the morning and the lowest level in the late evening.[81] Tyrosine hydroxylase, dopamine transporter, and dopamine D1- and D2-receptors all demonstrate this same circadian fluctuation.[54]

Iron is necessary for the production of tyrosine hydroxylase, the rate-limiting step in the production of levodopa, which is then decarboxylated to dopamine (Figure 4).[82] This takes place in the substantia nigra, where low iron levels have been identified in RLS.[57] Iron deficiency in test animals effects the dopamine transport system in pre-synaptic neurons in the striatum, resulting in a net decrease in the reuptake of dopamine and altered neurotransmission.[83]

Ferrous iron has the capacity to produce toxic hydroxyl radicals in neuronal tissue. Therefore, movement into and out of neuronal cells is tightly regulated by a series of iron transport mechanisms that allow iron to be exported out of the neuron into brain interstitial cells to prevent iron excess in neuronal tissue.[59] Iron storage in the brain can only occur via ferritin deposition in selected areas that do not include the substantia nigra or basal ganglia nuclei. Neurons in these areas contain the iron storage pigment neuromelanin that has a weaker iron-binding affinity than ferritin.[84] Because patients with end-stage renal disease who have RLS respond to I.V. iron administration, whether ferritin levels are normal or not, saturation of transport mechanisms may play a role in normalizing iron availability in neuronal tissue.[59]

Folate is also involved in the production of dopamine in the CNS. Folate, as 5-methyltetrahydrofolate, increases production of CNS tetrahydrobiopterin, a cofactor in tyrosine hydroxylase production (Figure 5).[85] Tetrahydrobiopterin also has a circadian pattern that modulates dopamine production – a daytime increase and an evening nadir.[86] These mechanisms may be responsible for the ability of folate supplementation to reverse RLS symptoms.

Conclusion

RLS is a movement disorder that affects a significant number of individuals with decreased levels of CNS iron or a familial disorder involving CNS dopamine production. The serious sleep disorder associated with RLS necessitates increased awareness among healthcare providers. Groups at risk for iron deficiency – the elderly, pregnant women, and individuals with end-stage renal disease – may need to be universally

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screened. Standard laboratory measures may not be sensitive enough to diagnose iron or folate insufficiency in the CNS. Nevertheless, the healthcare provider may need to address iron or folate supplementation in these patients. Nutritional supplementation may provide advantages to conventional dopamine-agonist medications that carry significant risk of side effects and do not address the underlying etiology of RLS.

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