Original Research Article

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Restless Legs Syndrome as an Early Neurological Manifestation of Vitamin B12 Deficiency

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Abstract

Background: Current hypotheses on pathophysiology of restless legs syndrome (RLS) implicate iron as a cofactor in dopamine synthesis. Vitamin B12 also plays an important role in dopamine synthesis, but its role in the pathogenesis of RLS has not been studied. We hypothesize that Vitamin B12 deficiency can potentially reduce the synthesis of dopamine and thus RLS may be an early manifestation of this deficiency. *Aims:* To measure serum vitamin B12 levels in patients with RLS and assess the response of RLS to its replacement. *Methods and Material:* To test this a Prospective, Open Label, Non-Randomized clinical Study was conducted. Fasting serum Vitamin B12 levels were measured in 44 consecutive patients who fulfilled the International RLS study group criteria. The response of RLS to dopamine agonists and to additional Vitamin B12 replacement therapy in those with low B12 levels, was measured. *Results:* Low serum Vitamin B12 levels (<211 pg/mL) were detected in 45% of patients with RLS. Those with normal B12 levels had a longer duration of symptoms, female preponderance and greater likelihood of positive family history. They were more likely to have a relapse of RLS symptoms after withdrawing dopamine agonists. Those with low vitamin B12 levels had shorter duration of illness, no gender preference, no family history and could be rapidly weaned off dopamine agonists without worsening of RLS symptoms, after B12 supplementation. None of the patients with low vitamin B12 levels had classical manifestations of B12 deficiency. *Conclusion:* As a significant number of our patients with RLS have low Vitamin B12 levels and respond well to its replacement, we propose that RLS may be an early neurological manifestation of vitamin B12 deficiency.

Keywords: Restless Leg Syndrome; Vitamin B12 Deficiency; Clinical Manifestation.

Introduction

Restless legs syndrome (RLS) is a well-defined condition characterized by an urge to move the limbs, usually associated with paresthesia, with clear nocturnal exacerbation and significant relief by limb movement [1,2]. This is a common condition, with prevalence rate ranging from 5 to 15 % in adults [3]. However, it is often under recognized or misdiagnosed due to lack of awareness among clinicians. RLS may occur as an idiopathic, often hereditary condition (primary RLS), or in association with several medical conditions (secondary RLS) like iron deficiency, diabetes mellitus, end stage renal disease, liver disease, pulmonary hypertension, celiac disease and Crohn's disease, gastric surgery and chronic obstructive lung disease [4]. Neurologic conditions associated with RLS include migraine, Parkinson's disease, spinocerebellar ataxias 1, 2, 3 and multiple sclerosis [5,6].

There are well validated diagnostic criteria for RLS [2] but their main shortcoming is the lack of well validated biological marker. Thus the diagnostic criteria heavily rely on clinical phenotyping.

The various biological mechanisms underlying RLS are still poorly understood. Hypotheses and evidence concerning the pathogenesis of RLS have so far focused two major lines of inquiry. First is on largely metabolic abnormalities mostly involving iron and the consequences of iron deficiency and second on the functional dopamine deficiency [7].

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Studies have found a range of other possible biological abnormalities in differing neuroanatomic region s producing the RLS state, including the opioid, serotonergic, and glutamatergic systems. But these have somewhat limited scientific support [8,9]. RLS like other common diseases may have multiple pathways to disease, some less common than others. Currently, however, there is no direct evidence to support any specific cause of these pathologic observations.

It is well known that vitamin B12 also plays a role as a cofactor in the pathways involved in the synthesis of dopamine [10,11]. However, there have been few published studies on vitamin B12 status of patients with RLS. Therefore, we undertook this study to evaluate if a subset of patients with RLS have vitamin B12 deficiency as an etiological factor.

Aims & Objectives

1. To estimate fasting serum vitamin B12 levels in patients with RLS.
2. To assess the response of RLS symptoms to vitamin B12 replacement therapy in those with confirmed deficiency.

Methodology

This prospective, observational and open label, non-randomized study was conducted in the Department of Neurology, at a tertiary care hospital in south India, over a period of 6 months. Consecutive patients with symptoms suggestive of RLS were evaluated with detailed history, physical and thorough neurological examination. This included description of RLS symptoms, their duration and severity (by visual analogue scale), sleep disturbances, leg movements in sleep, family history, previous and current drug use, details of previous consultations and diagnoses made, history of cognitive decline, and history of psychiatric symptoms. Diagnosis of RLS was established using the international RLS study group criteria.Patients with akathisia, RLS in pregnancy and those with drug induced RLS were excluded from the study.

Following investigations were done in all patients: hemogram, peripheral smear, fasting blood sugar, urea, creatinine, electrolytes, thyroid stimulating hormone (TSH), ferritin levels and vitaminB12 levels. NCS studies were planned for patients who had clinical signs of neuropathy. Fasting serum vitamin B12 levels were measured by Chemiluminiscence Immunoassay method (normal reference range of 211- 914 pg/ml).

Patients with confirmed low vitamin B12 levels were administered injection vitamin B12 1000µg intramuscularly or intravenously, daily for 1 week, then weekly for 4 weeks and thereafter monthly for 6 months. Patients with low ferritin levels were given oral iron replacement therapy. In all patients, dopamine agonists (pramipexole or ropinirole) were given for 3 months and stopped if RLS improved substantially (> 75% on visual analogue scale). These drugs were restarted if RLS symptoms recurred during follow up (Figure 1). All patients were followed up at 1 month, 3 months and 6 months.

Statistics

Continuous data was described as mean and standard deviation. Categorical data was described as numbers and percentage. Data were compared between two groups using Chi square test for categorical data and by student's t- test for continuous data. Mann–Whitney U test, a non-parametric test was used to compare between the two groups on data following non-normal distribution. A p value of <0.05 was considered statistically significant.

Results

Forty four consecutive patients with RLS were included in the study over a period of 6 months. Their age ranged from 12 years to 69 years (Mean 42.06±11.4 years). There was a female preponderance with female: male ratio of 1.4. The mean duration of symptoms of RLS was 82.9 months (range 1-300 months). Sleep disturbance due to RLS was reported in 52% of patients. Periodic limb movements in sleep (PLMS) was reported in 11%. An average of 3 previous consultations was sought elsewhere by our patients before reaching the correct diagnosis. Previous diagnoses made by primary care physicians included peripheral neuropathy, radiculopathy, myalgia, arthralgia, fibromyalgia, depression, anxiety, somatoform disorder and malingering. Coexisting medical and neurological conditions included anemia in 11patients (25%), diabetes mellitus in 10 (22%), hypertension in 11 (25%), hypothyroidism in 2 (4%), chronic renal disease in 1 (2%), Parkinsonism in 2(4%), stroke in 2 (4%), spinocerebellar ataxia type 1 in 2 patients (4%) (Mother and her daughter), lumbosacral disc disease in 4 (9%), and alcoholic

peripheral neuropathy in 1(2%). The two groups also did not differ in above medical co morbidities except that CKD and SCA were seen in those with normal Vitamin B12 levels. The type of sensory symptoms of RLS and strategies used by our patients to relieve them are shown in figures 2 and 3 respectively.

20 (45%) of our cohort had low vitamin B12 levels. Low ferritin levels were noted in 14 (31%) patients. 7 (15%) of our patients had both low ferritin and vitamin B12 deficiency.

We subdivided the entire cohort into two groups (Figure 1), those with normal vitamin B12 levels (Group A, 24 patients) and those with low B12 levels (Group B, 20 patients). The two groups differed in certain parameters (Table 1). In group A, there was a female preponderance (female: male ratio was 1.66),and the mean duration of symptoms was longer (mean of 82.9 months, median 12 months, range 2 months to 300 months). Family history of RLS in first degree relative was reported in 4 of these patients. In group B, there was no

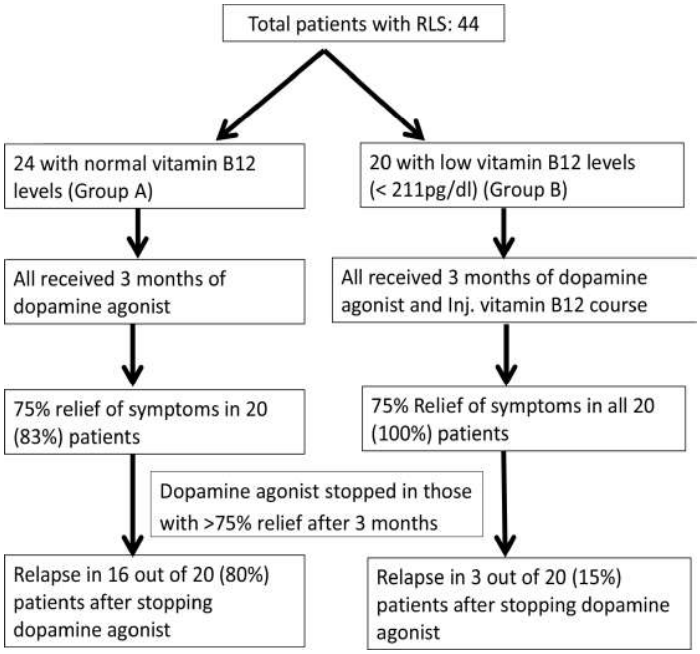

Fig. 1: Study Flow Diagram

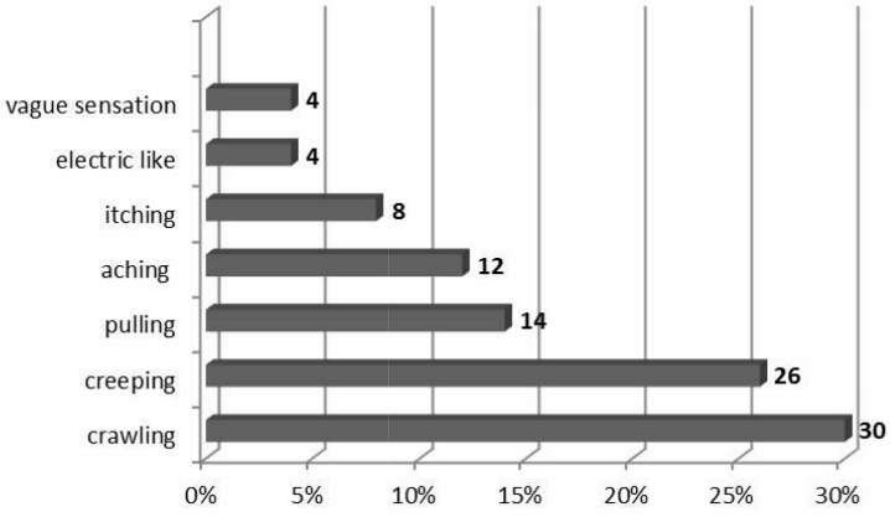

Fig. 2: Frequency of various types of sensory symptoms in RLS

gender preference (female: male ratio was 1), the mean duration of symptoms in this group was shorter (mean 21 months, median 12 months,range 1 month to 120 months) and none of them gave a family history suggestive of RLS. In contrast to group A, vitamin B12 levels ranged from 64 to 201 pg/ml (Mean 148.71±27.41 pg/ml) (Figure 4). None of these patients with low B12 levels had overt clinical manifestations of vitamin B12 deficiency like peripheral neuropathy, optic neuropathy, myelopathy, cognitive decline or psychiatric disorders. 70% of these patients were vegetarians, but consumed milk or milk products regularly.

The two groups also differed in their response to treatment. Substantial relief (>75% on visual analogue scale) was noted at 3 months in 20 (83%) patients in group A and in all 20 patients in group B (100%). This difference is not significant. After discontinuing dopamine agonists at 3 months, relapse of symptoms was noted in 16 out of 20 patients (80%) in group A and 3 out of 20 (15%) in group B ($p < 0.05$). Patients who received vitamin B12 had attained >75% relief in a mean of 2.6 months while the rest had same degree of relief by a mean of 3.1 months ($p>0.05$).

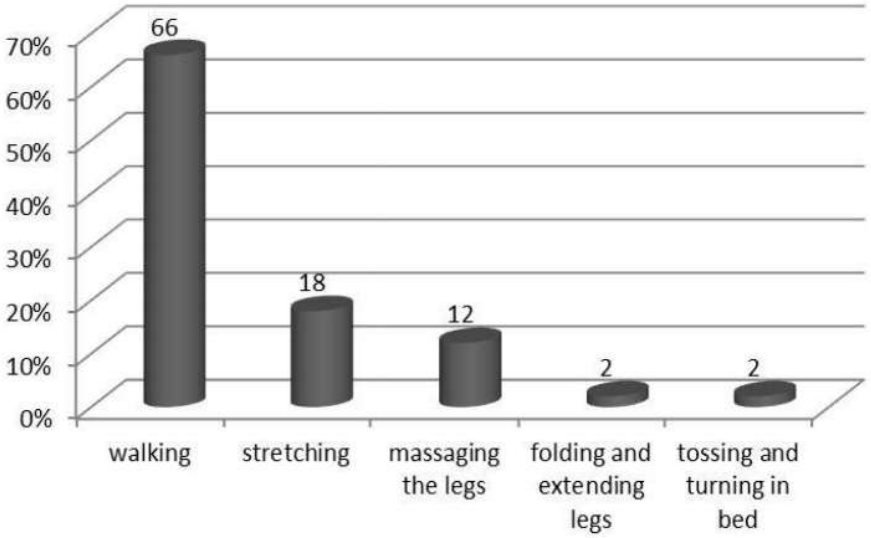

Fig. 3: Strategies used by patients to relieve RLS symptoms

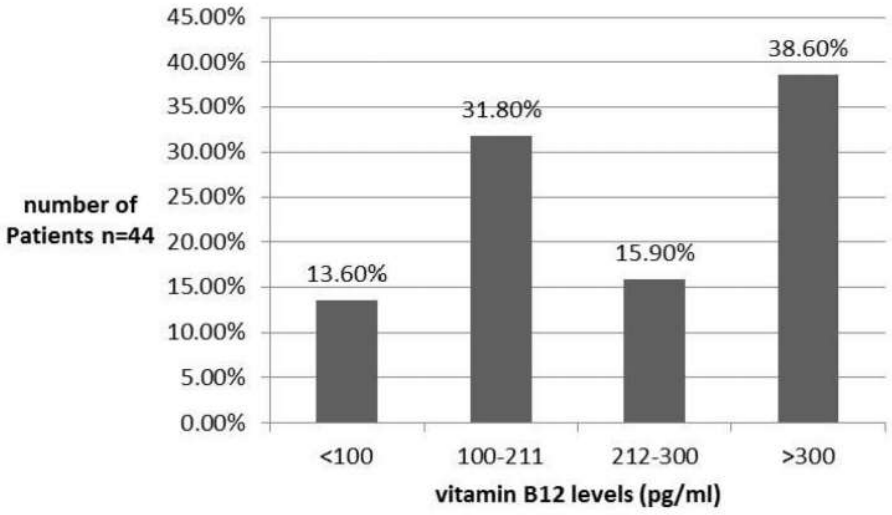

Fig. 4: Distribution of vitamin B12 levels in patients with RLS

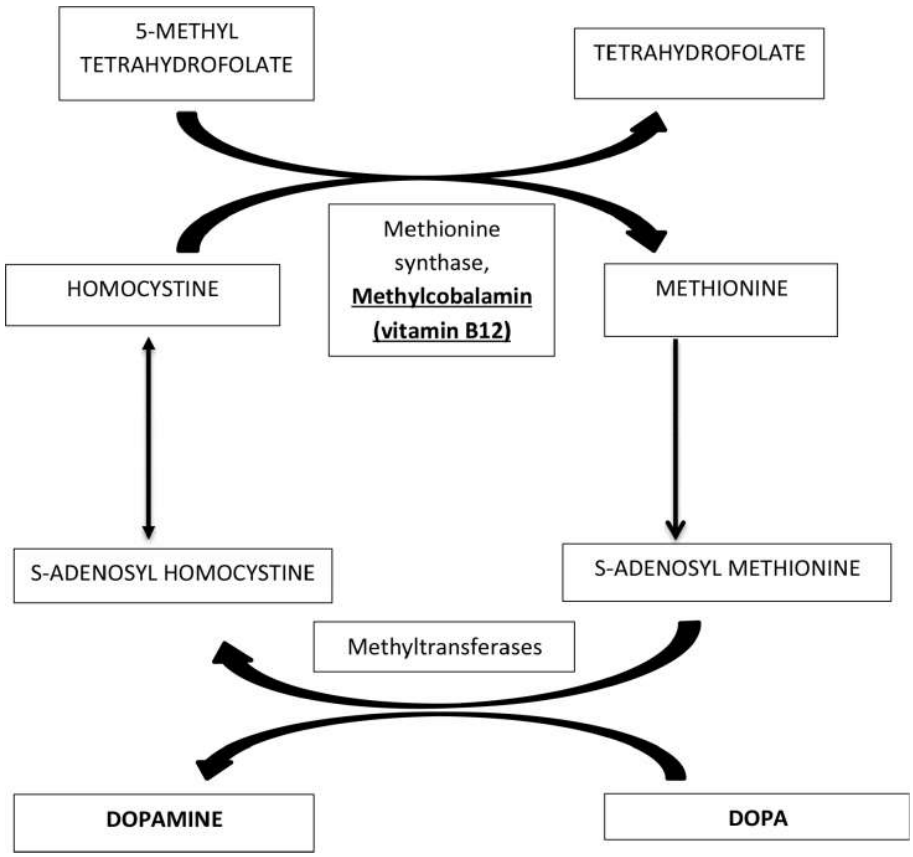

Fig. 5: Role of vitamin B12 in dopamine synthesis through methylation cycle

Discussion

In the present study, we detected low vitamin B12 levels in 45% of patients with RLS. This proportion is substantially higher than that in the general population in this region (16%) (12) ($p < 0.001$). Low ferritin levels were detected in 31%. As a group, those with low B12 levels differed from those with normal levels. Those with normal vitamin B12 levels had a longer duration of symptoms, a strong female preponderance, and more often had a first degree relative with RLS. They also suffered a relapse of RLS symptoms after withdrawing dopamine agonists. These are the typical characteristics of idiopathic RLS. In contrast, those with low vitamin B12 levels had a shorter duration of symptoms, had no female preponderance, and had no familial occurrence. They could rapidly be weaned off dopamine agonists without subsequent exacerbation of RLS symptoms. These observations suggest that the low vitamin B12 levels detected in our patients may not be a chance occurrence but indeed may have a pathogenic role. O'Keeffe et al reported dramatic improvement in the RLS symptoms in a single patient after Vitamin B12 replacement [13].

However, in a study by Bachmann et al., no difference in vitamin B12 levels were found between RLS patients and controls [14]. This discrepancy probably reflects the regional differences in the prevalence of B12 deficiency. In certain populations with high prevalence of B12 deficiency, it probably accounts for a significant proportion of RLS.

The classic neurological manifestations of vitamin B12 deficiency are subacute combined degeneration of the cord (SACD), peripheral neuropathy, optic neuropathy, cognitive impairment, psychiatric manifestations and involuntary movements [15,16]. Interestingly, none of our 20 patients with B12 deficiency had any of these manifestations, raising the possibility that RLS could be an early and the only manifestation of vitamin B12 deficiency that may predate other classic syndromes. Recognizing the deficiency and instituting vitamin B12 replacement at such an early stage is obviously desirable. Our vitamin B12 hypothesis in RLS is also supported by

the existing knowledge of the disease. There is considerable evidence that dopaminergic system is central to the pathogenesis of RLS [7]. Electrical [17] and pharmacologic [18] manipulation of dopaminergic A11 cell group of posterior hypothalamus have anti nociceptive effect and also suppress neuronal hypersensitivity. Moreover, experimental animals with lesions in the same area manifest with features typical of RLS [19]. Dopamine agonists are highly successful in abolishing RLS symptoms [7]. Therefore, it is plausible that an alteration in any step in the dopamine synthetic pathway has the potential to reproduce RLS symptoms.

It is interesting to note that vitamin B12 is required as cofactor in dopamine metabolism (Figure 5). It plays a key role in the methylation cycle by promoting conversion of homocysteine to methionine, which in turn is converted to S-Adenosyl methionine (SAM). SAM is an important methyl donor during methylation of biogenic amines including DOPA bymethyltransferases [11]. Also, accumulation of S-adenosylhomocysteine in the brain may also result in inhibition of transmethylation reactions [10,11]. Alternative homocysteinere-methylating enzyme, betainehomocysteine methyl transferase, is not available in brain. Thus, SAM accumulation causes inhibition of DNA methylation reactions. This inhibition of methylation reactions can affect a great number of biochemical processes and can result in decreased production or metabolism of many substances including enzymes and proteins involved in dopamine and iron metabolism in brain [10].

Thus, vitamin B12 deficiency can potentially reduce the synthesis of dopamine and cause RLS symptoms. As low vitamin B12 levels are common in India [12], mere detection of low levels does not establish an etiological role in RLS. However, a prompt and consistent therapeutic response as noted in our patients considerably strengthens the hypothesis that vitamin B12 deficiency can manifest with RLS. This hypothesis needs to be tested in a larger sample on a longer follow up study with a blinded design.

Our study has some limitations. The sample size is small, the duration of follow up is short. Polysomnography was not done to diagnose PLMS as it is a supportive criteria and has no specific clinical significance except its association with RLS and its severity. Also, vitamin B12 levels were not obtained after replacement because serum cobalamine levels rise instantly regardless of cobalamine effectiveness [20]. Also, Methyl malonic acid levels and serum homocysteine levels were not done as these are required to establish true vitamin B12 deficiencyonly if B12 levels are between 200-350 pg/ml [20].

Further Implications

As a common disease, RLS is not homogeneous but rather a spectrum that may have different subtypes. The key to uncovering the RLS mystery may lie in the correct decoding of symptoms that drive movement. Multiple other diseases associated with RLS (secondary RLS) give a clue in discovery of newer pathophysiological pathways. But with the exception of systemic iron deficiency, little has been learned to date. There needs to be continuous research about the pathophysiology of RLS and search for a biomarker, either genetic, serologic, or any other body fluid. Vitamin B12 levels may be one such biomarker in pathophysiology of subset of RLS patients in specific geographical regions. Clinical, animal, genetic, and cellular models should be included in future studies. Both clinicians and basic researchers will be essential in the effort to determine the underlying causes of RLS.

Conclusion

Even with decades of research at most basic level, an explanation for what causes the peculiar symptoms of RLS, that are so central to its clinical identification, is still lacking. A significant proportion of our patients with RLS have low Vitamin B12 levels. Vitamin B12 replacement therapy in these patients helps in prompt relief of RLS and permits withdrawal of dopamine agonist agents. RLS could be an early clue to Vitamin B12 deficiency well before other neurological manifestations. But as with all new discoveries, this leads to more avenues of research.

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Declaration of interest: None

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