REVIEW ARTICLE

Restless legs syndrome

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Abstract

Sleep is essential to maintain quality of life. Restless legs syndrome (RLS) is a disorder which is characterized by uncomfortable feeling in legs, irresistible urge to move them and compromised sleep quality. It is a common problem but is usually under diagnosed or misdiagnosed. It can be easily diagnosed by using criteria proposed by International Restless Legs Society. Though no specific investigations are require for diagnosis, investigations are required to discern the cause. Treatment of the cause relieves the symptoms of secondary RLS. In case of primary RLS most patients improve with non-pharmacological treatment. Those who require drug treatment should be classified as per frequency and severity of symptoms. Dopamine agonists are first line drugs, however, the treatment needs to be individualized depending upon the symptoms of the patients. This review aims at comprehensive overview of RLS including diagnosis and management.

Keywords: Restless legs, RLS, sleep disorders, Willis Ekbom Syndrome

Introduction

Sleep is an essential human behaviour. Insomnia as a sleep disorder is prevalent, in at least 10-20% of the population meeting stringent diagnostic criteria,[1,2] and in as many as 50% presenting with symptoms suggestive of insomnia but not meeting the diagnostic criteria.[3] The disorders which interfere with sleep compromise the quality of life and productivity of the individual. Restless legs syndrome (RLS) is one such disorder which interferes with sleep and may render an individual unable to function during the day. It is characterized by an uncomfortable feeling, usually but not exclusively, in the lower extremities that leads to an uncontrollable urge to move. It begins or worsens during the periods of rest, deteriorates during evening or night time hours and is partially or totally improves with movement. It has a strong circadian sway that may have profound effect on the sleep quality. Winkelman et al, in a cross-sectional community based study showed that patients with this disorder have longer sleep latencies and higher arousal index (20.1 vs. 18).[4] Sleep latencies increased progressively as the RLS symptoms increased. Not only this, subjects with RLS reported deterioration in health-related quality of life (HRQOL) in all physical domains as well as mental health and vitality domain.[4] RLS has a large impact on quality of life at par with that of type 2 diabetes mellitus and osteoarthritis.[5,6] Emerging data suggests that RLS is also associated with metabolic dysfunction, autonomic dysregulation and increased risk of heart diseases.[7] A systematic review has shown that syndrome predisposes to high risk of cardiovascular disorders, diabetes, impaired glucose tolerance and has shown modest association with body mass index and dyslipidemia.[8] It not only affects the patient's life but also life of the bed partner who experience kicking or leg jerks of the RLS patient. Hence it is of utmost

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importance to recognise and manage this problem early and judiciously so that the patient as well as the bed partner can have a better quality life.

Restless legs syndrome was first reported in literature as early as seventeenth century by Thomas Willis, who expressed it as "Two discourses concerning the souls of brutes". The description captured the essence of the disease, relating all four components; sensory symptoms, motor symptoms, involuntary movements and sleep disturbances.[9] However, the term "Restless Legs" was coined by Karl Ekbom in 1945. He did pioneering work in this disease and collected a large data and highlighted the key diagnostic features. Later he also described the restless leg in association with pregnancy and iron deficiency anemia and introduced this disease to the world of Medicine.[10] An International RLS Study Group (IRLSSG) was formed in nineties. In 1995, the newly formed IRLSSG proposed and published a set of criteria for diagnosis which were refined in 2003.[11,12] Since then research has shown RLS as a common and extremely disturbing disorder. (Figure 1) This treatable entity is not well recognized by the physicians because of lack of awareness and absence of a diagnostic test. In a study done in United States and five European countries 81% patients with symptoms of RLS discussed their symptoms with a primary care physician but only 6.2 % were given the diagnosis of RLS.[5] Results were similar in an international survey in which only 12.9% of reported subjects were given a diagnosis.[13] It is often misdiagnosed as back pain, depression or anxiety.[5] More often than not these patients visit various health care providers mostly physicians and orthopedicians, even neurologists without a diagnosis.[13]

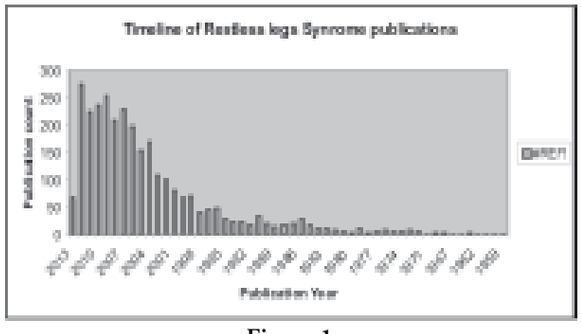

Figure 1

Source: The U.S. National Library of Medicine (with permission)

The extension of newly proposed and rewritten criteria of diagnosing RLS by IRLSSG to general population is required to diagnose this disorder and improve the quality of life of these patients. RLS can be idiopathic or secondary. Idiopathic disease has strong familial inheritance and family history is present in 18.5 to 59.6 % of the patients.[14,15,16] It is associated with variety of conditions; most common of which are iron-deficiency anemia, uremia on hemodialysis and pregnancy.

Epidemiology

RLS prevalence in general population is 2.5-15 %, however, it varies with studies depending upon the criteria used by various authors. Some studies, which used a single question to diagnose RLS have found higher prevalence as compared to studies with more rigorous criteria for the diagnosis.[17] Ekbom in his dissertation reported prevalence to be 5%.[10] More recent studies have reported that as many as 10% of the population in Europe suffers from RLS.[18,19]

Prevalence of RLS is lower in India and its neighbouring countries as compared to that in the Western hemisphere. In India about 0.8% of the population are reported to be suffering from symptoms pertaining to RLS.[19] This may be due to lack of accurate diagnosis or lack of awareness. In a study done by Gupta R et al, a much higher prevalence (15.31%) is found among the patients who visited psychiatry or neurology OPD's with leg pain or insomnia.[20] No population based studies are reported from the Indian subcontinent, hence it is difficult to know the true prevalence. It affects all ages but the prevalence increases with age. About 2% of children suffer from RLS and many adults report symptoms from as early as 10 years of age.[21, 22] Women outnumber men by a ratio of 2:1 in Western as well as in the Indian data. It is the most common movement disorder during pregnancy affecting 13.5 to 26.6% pregnant women.[17] Women experiencing transient RLS during pregnancy have four times more chance of being affected with the ailment later in life.[23]

Primary RLS

It is an idiopathic form of the disease with no known cause. Three hypotheses have been proposed; first is the up-regulation of brain's nigrostriatal dopaminergic system as in Parkinsonism.[24] Second theory is based on

dysregualtion of iron metabolism. Brain biopsy has shown low iron concentration especially in dopaminergic neurons of patients with RLS which leads to fewer iron receptors responsible for formation of neurotransmitter dopamine.[25,26] Third is with reference to the genetic factors. RLS has been observed to run in families. From 2001 to 2006, five different genetic linkages (RLS 1 to RLS 5) were reported.[27] In the year 2007, two groups reported three different associations working on genome wide case association studies.[28,29] Till date the relationship between susceptibility variants and biological determination of RLS is ill-understood. RLS1 gene with its locus on chromosome 12 is found in multiple families with RLS and is a field of interest for further research.[27] Primary RLS usually presents before forty years of age.

Secondary RLS

It occurs in association with other medical conditions such as iron deficiency anemia, pregnancy and end-stage renal disease on hemodialysis. Prevalence rate of RLS in patients on haemodialysis was found to be between 20 to 50%.[30-32] Study done in India by Bhowmik D et al in dialysis patients showed the prevalence of RLS to be 6.6 % which was much lower than in the West.[33] The onset of symptoms of secondary RLS typically begins after 40 years of age. The clinical course is rapidly progressive and escalation of symptoms occurs coinciding with the causative factor. In all the three conditions it was seen that RLS symptoms reverses with reversal of primary condition (e.g. renal transplant in patients on haemodialysis).[31] The common feature in all these three conditions may be anaemia and/or iron status. However, most studies failed to establish significant difference between level of haemoglobin and iron indices of patients with renal failure or pregnancy suffering from secondary RLS patients as compared to those without RLS.[34,35]

Several other conditions have shown some association with RLS and the most important of those is peripheral neuropathy.[36] The type of neuropathy may alter the frequency of symptoms and RLS is found to be more commonly associated with sensory neuropathies.[36] Many other neurological disorders have shown some link with RLS such as spino-cerebellar ataxia, myelopathies, arthropathies, fibromyalgia and Parkinsonism. Studies have shown increase in symptoms of RLS in patients with rheumatoid arthritis.[37]

Evaluation of the patient

The diagnosis of RLS is difficult as patients not only describe symptoms differently (Table 1), but are also unable to understand the problem beyond compromised quality of life. At times patients of younger age group are unable to describe their symptoms beyond some uncomfortable feeling in their legs.

Table 1: Various Descriptions of Sensations in RLS

Aching	Itching
Burning	Jittery
Bubbling	Jimmy legs
Crawling	Pulling
Crazy legs	Shock-like feelings
Electric current	Tearing
Elvis legs	Throbbing
Fidgets	Tingling
Grabbing	Tightness
Heebie jeebies	Worms or insects moving

RLS should be considered in all patients with symptoms of sleep disorders including insomnia, pain in the legs or uncomfortable feeling in the legs relieved with movement. The core feature of this syndrome is irresistible urge to move the legs. Since there are no diagnostic clinical tests, a detailed history is very important. A history of drug intake should be elicited (Table 2). One should try to elicit a history of similar illness in family.

Table 2: Drugs Associated with RLS

1. Antihistamine: H1 and H2 blockers
2. Antipsychotics: Haloperidole, olanzipine and risperidone etc.
3. Anticovulsants: Phenytoin
4. Beta-blockers
5. Dopamine blockers: Metoclopramide, promethazine, prochlorperazine
6. Caffeine
7. Lithium
8. Antidepressants :
   a. Tricyclic antidepressants
   b. SSRI antidepressants
   c. Others such as mitrazepine and venalafaxine

RLS is a clinical diagnosis based on the criteria proposed by IRLSSG.(Table 3) In addition to the essential criteria, there are supportive features that can help in case of diagnostic uncertainty.

Table 3: Diagnostic criteria for RLS

Essential Criteria
1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night
Supportive Criteria
1. The presence of family history among first degree relatives
2. Response to dopaminergic therapy
3. Periodic limb movements during wakefulness or sleep
Associated Features
Onset can be at any age, patients are usually middle aged or older at presentationLeg discomfort or need to move result in insomniaLow serum ferritin(< 50 µg/L)

Source: The International Restless Legs Study Group [12]

Secondary RLS needs laboratory evaluation. If secondary RLS is suspected by history and clinical examination, investigations are required to establish the cause. (Figure 2)

Figure 2: Diagnostic Algorithm for Restless Legs Syndrome

A high index of suspicion is necessary to recognize this problem in pregnant women. As the obstetricians' main focus is on fetal growth and progress of pregnancy, they tend to disregard other symptoms. Therefore diagnosis of RLS requires active case finding and knowledge of the disorder so as to bring out accurate history and achieve a diagnosis.

Differential diagnosis

A problem which looks as non-descript as this, may have many differential diagnoses starting from back pain to peripheral neuropathy. (Table 4) This includes ruling out diseases such as peripheral neuropathies, vascular disorders, nocturnal cramps, arthritides etc. Patients with neuropathy can have typically similar sensory symptoms as RLS like tingling or numbness but it is different from restless legs as they are not associated with irresistible urge to move the legs. At the same time peripheral neuropathy does not follow any circadian rhythm. However, these two conditions may co-exist. Nocturnal leg cramps follows the circadian rhythm like RLS and are more prominent on rest but are associated with hardening of muscles which is absent in RLS. An urge to move all body parts occurs in akathasias but sensory symptoms characteristic of RLS are absent. Patients with a spinal cord or root lesion may have painful legs and toe movements (spontaneous flexion and extension of toes) but unlike RLS these are not associated with focal urge to move or a circadian rhythm. Contrary to RLS, vascular disorders worsen with activity and are associated with absent or decreased peripheral pulses and cold extremities. Arthritis is associated with pain localized to joints which worsens with activity and is associated with radiological abnormalities of joints. Periodic limb movement syndrome (PLMS) is essentially a sleep phenomenon and is not associated with any sensory symptoms. A sleep study is essential for the diagnosis of PLMS. In patients with drug-induced akathisia, it is usually a whole body feeling rather than the limb centred symptoms and it follows no circadian rhythm. A careful history taking and general neurological examination can rule out many of these conditions.

Laboratory evaluation

Although no specific investigations are required for the diagnosis of RLS, however, certain investigations are needed to establish secondary RLS. Polysomnography is

required if there is clinical suspicion of sleep apnea. Evaluation of iron status required to establish the relation to iron deficiency anemia. Only ruling out anemia is not enough, serum iron and ferritin levels are needed to rule out the role of iron deficiency. Suggested immoblization test (SIT) may become standard diagnostic test in future. In this test patient sits in a bed at 45 degree reclining position with feet outstretched. Any stimuli such as changing pictures or sounds are minimized for next one hour. Patient is asked to relax and keep legs as still as possible. Tightening of limbs to avoid moving is not allowed nor is patient allowed to sleep. The test lasts for 60 minutes. Rest duration acts as a stimulus for provoking RLS symptoms. Both periodic limb movements while being awake and sensory symptoms are reported. This test produces best results if performed at night. This is usually done in conjunction with and just before polysomnography. A full night polysomnography and SIT give objective evidence and assessment of RLS, providing direct measure of associated PLMS.

Treatment

The treatment of RLS is essentially dependent upon the etiology and severity of disease. First, if a secondary cause of RLS is discernable, treatment aims at management of the cause. After the cause of RLS is corrected, the symptoms of patients should be reassessed and if the patient still have distressing symptoms then only treatment specific to RLS should be offered. Second step should be to assess severity and frequency of the symptoms. Some patients experience symptoms only rarely or in association with aggravating factors such as prolonged immobilization like a long car ride or flights, for others it is a daily agony of not being able to sleep at night and urgency to move about. Hence, the symptoms may be defined as occasional, infrequent and disturbing. The frequency of symptoms prompts either intermittent or daily treatment.

Depending upon the severity of symptoms, treatment can be either pharmacological of or non-pharmacological. Patients with mild symptoms should be offered non-pharmacological treatment. Drug treatment should be offered only to patients who fit in the criteria for moderate to severe disease and should be tailored for the patient.

Extensive amount of literature has emerged on treatment of RLS in recent years. Evidence based guidelines are published by various societies such as task force for the Movement Disorders Society,[38] the European Federation of Neurological Science,[39] the International Restless Legs Study Group (IRLSSG)[40] and American Academy of Sleep Medicine.[41]

Non-pharmacological treatment

It mainly consists of good sleep hygiene. Patients should be advised a regular sleep schedule in a proper bed-room which is used only for sleeping and is quiet and dark. Hot and cold baths and mental activity (e.g. crossword puzzles) may also help.

Exercise may help some patients; hence they should be advised mild to moderate exercise. A randomized controlled trial by Aukerman et al to study the role of exercise in management of RLS showed significant improvement in exercise group as compared to that in the control group.[42] The mechanism by which exercise decreases RLS symptoms is not well understood.[43] Patients with RLS need to change their life style around the disease symptoms such as shifting sedentary activity to morning when symptoms are less where as activities which require movement to evening when symptoms are more pronounced.

Stimulant substances and those drugs which aggravate the symptoms including caffeine should be avoided. Drugs such as dopamine-blockers, many anti-depressants, neuroleptics and antihistaminics are the major culprits. (Table 3)

Pharmacological Treatment (Table 4)

Drug therapy is an alternative only when symptoms compromise quality of life, sleep and daytime functioning. It is designed to relieve the patients' sensorimotor symptoms and sleep disturbances. It is worthwhile to remember before starting the treatment that it is at best symptomatic not curative or preventive and most patient will require life long treatment. Patients need to be made aware of these issues, drug side-effects and then offered drug treatment. Only 20% of all patients require drug treatment.[44] Treatment options include dopaminergic agents (DA), anticonvulsants, opioids and benzodiazepines. The agents approved for RLS includes ropinirole, pramipexole, rotigotine and gabapentine enacarbil. Choice of agents depends upon form of RLS, associated clinical condition and individual tolerance. The drug dosage given to RLS patient should be strictly kept to minimum and maximal permissible dose should

Symptoms	First-line	Second-line	Third-line
Daily(mainly nighttime)	Dopamine Agonists Gabapentin	Low to medium potency opioids	Sedative-hypnotics
Daily (Night and day)	Long-acting dopamine agonist (Rotigotine)		
Infrequent symptoms	Levodopa	Dopamine agonist, sedative hypnotics	Low to moderate opioids
Painful RLS	Anticonvulsants		
With Sleep Disturbances	Sedative-hypnotics		
With Neuropathy	Anticonvulsants		
Refractory	Different dopamine agonist, different Class of drugs	Combination Therapy	Strong opioids

never be exceeded. It must be considered that drugs owing to their short half life do not cover 24- hour period and should only be administered in single doses few hours before usual time of symptoms which is usually in the evening. A single drug may not help and trial of several drugs may be needed. Treatment should be administered for sufficient duration to assess its effects on symptoms before switching to a different drug.

Occasional or infrequent symptoms

Augmentation is not a problem with intermittent use, hence dopamine precursor levodopa is the best agent for intermittent therapy. It is used in combination with carbidopa and doses range from 25/100 to 50/200 (mg carbidopa/ mg levodpa), usually taken two hours before symptom onset. Hypnotics like zolpidem (5-10 mg) or benzodiazepines like clonazepam are used to relieve sleep disturbance in patients who have inability to sleep as most prominent symptom. DAs such as pramipexole or ropiranole may also be used. Low to medium potency opioids such as propoxyphene, coedeine or tramadol are second line agents. Levodopa and opioids are useful when symptoms are unpredictable as these agents have more rapid onset of action making these useful for situational use. Dopamine agonist, however, should only be used for expected symptoms.

Daily symptoms

Daily treatment is needed for patients who have moderate to severe symptoms that compromise their quality of life everyday or on most days of the week. In such cases DA (pramipexole, ropinirole and rotigotine) are first line of treatment. Drugs should preferably be taken about 2 hours before expected onset of symptoms. Usually a single dose at bed time suffices for patients who have nightly symptoms. Those who have severe, significant evening symptoms should take a dose in early evening. Those patients who get morning symptoms associated with hours of inactivity may need long acting agents like rotigotine transdermal patches. These drugs should be started with a lower dose and gradually titrated upwards every 2-3 days to avoid gastrointestinal side effects and orthostatic hypotension.

The alternative agents should be considered for initial treatment only in case of contraindications to DA or when a specific clinical situation warrants use of a particular drug. For example RLS with neuropathy should be managed with gabapentin or pregabalin. Second line agents such as opioids are usually reserved for refractory RLS, or when the first line agents are contraindicated or there is no response to the same. Only low to medium potency opioids like codeine, hydrocodone and tramadol should be used.

Refractory Symptoms

RLS is termed as refractory when daily symptoms are not responding to treatment with at least two classes of drugs (one dopaminergic and other non-dopaminergic) in adequate doses and for sufficient length of time. Such symptoms should be managed by sleep specialists only. First, a trial of a different DA may be adequate. If an approved DA is inadequate, an unapproved drug such as alternate dopaminergics, anticonvulsants or opioids may be tried. Intermittent drug holiday or drug rotation may be considered with the drug free period covered by a different dopamine agonist or opioids. If that does not helps then switch to an opioid or anticonvulsant whichever is not yet tried. Other options are combination therapy depending upon the symptoms. High potency opioids

such as methadone (5-40 mg/ day) are reserved for severe resistant symptoms. Other strategies include using higher doses for control of symptoms. This can be counter productive as it can increase the problem of augmentation. Changing the timing and the frequency of doses may also help.

Pharmacological agents

Dopaminergics

Akpinar and Montplaisir et al first reported response to levodopa.[45,46] Subsequent studies have found that levodopa and dopamine agonist consistently give high response rates. These agents quickly ameliorate the symptoms but have significant side effects later due to augmentation i.e. occurrence of symptoms earlier in the day; increased severity of symptoms and spread of symptoms to the other parts of the body.[47,48] Levodopa augmentation rates are reported to be as high as 66%.[49] Currently it is recommended for those patients who have intermittent symptoms and require only sporadic therapy. With advent of dopamine agonist for RLS, augmentation rates became as low as 20-30% with persistent relief in symptoms. A recent Cochrane review showed that dopamine agonists were superior to placebo in randomized control trials. These are now first line therapy for RLS.[41] Currently three dopamine agonists are approved by FDA, pramipexole (0.125 to 075 mg), ropiranole (0.25 to 4 mg) and rotigotine (1-4.5 mg). Dopamine agonists are required in significantly low doses in RLS as compared with Parkinsonism. Augmentation is still a significant problem even with the newest dopamine agonist. In such a case, patient can be advised to alter the timing of the dose to an earlier in day. If there is no response with these measures, patient should be shifted to another dopamine agonist or another class of agents. Other known side-effect with this group of drugs may be impulse control disorders such as pathological gambling, compulsive shopping, compulsive eating and hypersexuality. This side-effects warrant stoppage of the drug. There are no head to head trials comparing various dopamine agonists. Pramipexole is used for moderate to severe RLS while ropiranole is also effective against severe to very severe RLS.[41] Rotigotine is available as transdermal patch. This is a relatively new drug which is found to be effective in RLS in many robust studies with consistent results.[50-54] The doses ranges from 1 to 4.5 mg with increasing effectiveness at about 3 mg.[53]

Ergot derived dopamine agonist like pergolide and cabergoline are not recommended in routine clinical practice because of risk of cardiac valvular fibrosis and other fibrotic side effects. Cabergoline is only recommended if other agents have failed after reasonable trial and with close clinical follow up.[41]

Anticonvulsants

Gabapentin enacarbil is recent FDA approved addition to the armamentarium against RLS.[41] Various studies have reported change in RLS score with this new drug.[55-58] In a double blind placebo controlled trial it has been reported to reduce both symptoms of RLS as well PLMS.[59] It has been found particularly efficacious in treatment of RLS associated with sleep disturbances. Movement disorder society has found that other agents such as carbamazepine, sodium valporate, and pregabalin are probably efficacious.[60] Augmentation has not been reported with gabapentin enacarbil. As with dopaminergics it is recommended in single night time dose however in patients with more severe evening symptoms, it can be given in two divided doses. It is particularly recommended for RLS associated with painful neuropathy. It is generally well tolerated, most common side-effects being somnolence and dizziness. It is recommended for moderate to severe RLS.

Medications acting on adrenergic systems

Clonidine, presently has minimum supporting data for its use in treatment of RLS. There are only 2 studies with 11 and 20 patients that have studied clonidine compared to placebo and have found it to be effective.[61,62] It is associated with frequent side-effects, however, may be considered in treating hypertension and RLS concurrently.

Opioids

Opioids are known to be effective for RLS since 17th century when Willis described it first. Since then opioids are frequently used in management. There is meagre data to support opioids, two studies were done oxycodone and propoxyphene, which showed effectiveness opiods in RLS.[63] These are effective for the patients who are not relieved by the other treatment. Other opioids like codeine, hydrocodone, methadone, and tramadol have also been used. Longer acting drugs like methadone often help severely affected patients who have failed dopaminergic therapy.

Benzodiazepine

Clonazepam is tried in the management of RLS. [64]Currently it is not recommended as sole agent,

however, it can be use as adjunct as its mechanism of action is different from that of dopamine agonists.[41, 65]

Treatment of secondary RLS

It aims at treatment of the cause leading to RLS. Most common causes are iron deficiency anemia, end-stage renal disease requiring dialysis and pregnancy. In all the three conditions, correction of the disorder (normalization of iron status, renal transplant) results in relief in RLS symptoms. Only correcting anemia is not enough, iron stores should be restored. Patients with serum ferritin of less than 112 pmol/L (50µg/L) should be started on iron supplements.[66] Studies have tried to demonstrate a common link between the three conditions which is thought to be either anemia or iron deficiency. One study has shown that RLS symptoms improve with normalization of iron stores by erythropoetin replacement in hemodialysis patients.[67] However, no study has demonstrated significant differences in iron stores of RLS patients as compared with control either in association with hemodialysis or pregnancy.[68, 69]

Drug induced RLS should be also be kept in mind and first managed with the withdrawal of the offending drug. In general potentially treatable underlying diseases should be looked for while managing a patient with RLS (Figure-3)

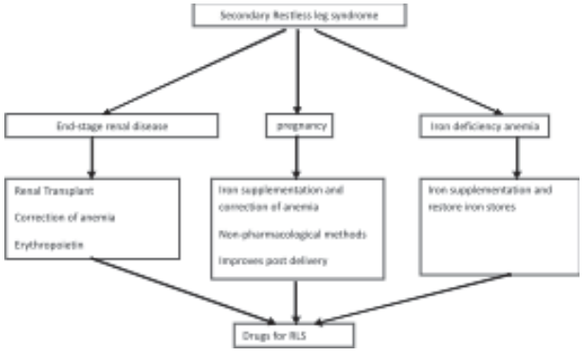

Figure 3: Management of Secondary Restless leg syndrome

Conclusion

RLS is an uncommonly diagnosed common disorder which affects the population at large. If diagnosed and managed properly it can substantially improve quality of life of patients as well as bed partners. Active case finding should be done at least in the special population such as pregnant females and patients with renal failure. Diagnosis is essentially clinical, based on criteria given by International Restless Leg Society. Polysomnography is not needed for the diagnosis unless PLMS is suspected in its association. It can be effectively treated with small doses of drugs without significant side-effects. Augmentation is most common side-effect. This has reduced with advent of newer drugs. Secondary cause should always be looked for and treated before starting pharmacological treatment.

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