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Review Article

Restless Legs Syndrome, the Pitfall: Hardly Diagnosed and Rarely Treated Neurological Disease

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Abstract

Restless legs syndrome is a chronic progressive sleep associated sensory motor disorder which develops within the neurological disorders like Parkinsonism, Neuropathy pain and possible dementia. The global prevalence of restless legs syndrome is increasing day by day and research studies have been reported the essential need for research in specific diagnosis and treatment of restless legs syndrome. Prevalence of Restless legs syndrome is more in Female and pregnant women than men in the almost whole world. In India and many other countries of Asia and throughout the world the term Restless legs syndrome (RLS) is still a questionnaire. It is reported many a time by the Physicians, Neurologists and Gynecologists as a mal-diagnosis of Restless legs syndrome in India and in others countries also. The exact pathophysiology of the RLS is still not clear, but some superficial assumptions regarding the progressions of disease and root of disease through the gene molecular concepts. Few Traditional Chinese medicine and allopathic medicine have been reported a successful treatment of RLS, but it is either symptomatic or depends on time management. Dopamine Agonist and opioids are possible symptomatic treatment for RLS, but no treatment is available if it has entered in a severe stage of RLS. Relations to the lower cerebral ferric and Dopamine levels are probably reported as the cause for Restlessness like, although genetic biomarkers have been developed for the diagnosis of the disease. The core treatment of the disease is still under discovery. Early diagnosis of the disease can make difference in the first line treatment.

Keywords: Restless leg syndrome; Parkinsonism; Neuropathy; Preeclampsia; Dopamine antagonist; Ferric ion; Pregnancy; Periodic limb movement disorder (PLMD)

Introduction

Restless legs syndrome (RLS) which is also known as wills Ekbom Disease (WED), Wittmaack Ekbom disease is complicated hardly diagnosed neurological disease which vary with symptoms and degree of morbidity [1]. As per the guidelines of National Institute of Neurological Disorders and Stroke (NINDS), Restless Legs Syndrome is a medical condition characterized by unpleasant sensations in the legs, including burning, tugging, and tightening, and feels like insects crawling inside the legs. British anatomist and physician, Thomas Willis in the 17th century stated the first clinical description of RLS and later on in 1945 Swedish neurologist Ekbom, characterized the neuropathological syndrome more specifically. Now a days with more based on research data it is considered as more organic brain disease than systemic brain neurodegenerative disorder based on dysfunction of the neurotransmitter system of dopamine and iron signaling in brain with a unknown genetic mutation which modulate the metabolism of iron with different degree in brain and substantial space. RLS is a neurological sleep associated sensory motor cognitive disorder that makes urge to move legs continuously [2,3]. It makes difficult to get sleep due to uncomfortable urge of moving legs. Sleep is disturbed due to unknown pathology in brain including lowering the Grey and white matter, fluctuated iron levels in brain which affects the dopamine levels in SN [4]. The symptoms gets worsen most at night and individual can't sleep well [5]. Most of the time it gets difficult to explain about the restless legs event happened at night. Due to this REM and NREM cycle is disturbed and hence it affects most of the normal physiology of brain. Individual feel day time weakness, Body ache, depression like behavior, Sleep during day, irritability, Swings of mood, Confusion like symptoms and if there are presence of any associated systemic disease like kidney disease, anemia, respiratory disease like arthritis, blood disorder or metabolic disorder, pregnancy, epilepsy then it get worsen a lot and affects at highest degree of quality of life [6-8]. Research in Restless legs syndrome has been approached many a times with animal models but there is no significant model developed which mimic the same exact mechanism involved in it. So that further targeted research to understand the exact reason of RLS should get focused. There are mainly two types of RLS are defined up till yet, one is at the early stage of life before 45 and second is after 45 years of age which is more worsen progressively. Early or Primary RLS is very complicated and difficult to diagnose [9]. Primary RLS affects total quality of life progressively with no identified cause and mal diagnosed as growing pain in children that is why it is categorized as idiopathic more often [10]. The RLS is a complex neurological sleep disorder which involves many physiological symptoms which confuses with other pathophysiology like Parkinsonism more often hence misdiagnosed and mal treated more often [6].

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Epidemiology

RLS is hardly diagnosed as silent symptoms or confusing symptoms with many neurological and vascular diseases. Hence prevalence of RLS is reported very less worldwide. More often the reported prevalence is not sure to be the exact figure as it remains undiagnosed in many countries globally [11]. The prevalence of RLS is reported in India is about 2-5% and other Asian countries. There were no surveys done in India to measure the prevalence of RLS as it is neglected diagnosis most of the time. Although, few clinical trials and research studies have shown 1.5-6.6% in Indian population. In India its ratio was found to be more in males than female according to one study made in hospital. Usually a higher prevalence is found in females than in males, and increasing in frequency with older age worldwide studies. According to American data RLS affects 2.5-15% of American population. In comparison to Caucasian to African countries it is found more prominent in Caucasian with higher ratio in females and children comparison to male. As per data suggests it has shown 3% prevalence of RLS in Middle Eastern population [12,13].

Prevalence based on clinical trials and research done on RLS

According to the National Sleep Foundation Report in 1998, about 1/4th pregnant females develop Restless legs Syndrome in their 3rd trimester and disappears within the first month after delivery in most cases [11]. Most of the studies has shown 2:1 ratio among females in comparison of men. RLS is the most common neglected diagnosis during pregnancy in anemic conditions. In Ancient Research Based Clinical Studies of RLS had shown RLS like symptoms in 500 women at 33-34 weeks' gestation and 4 weeks after delivery. Observed prevalence of RLS in those females was 19.5% which is more likely attentive than any other disease in women. Severity of RLS was, observed only in seven women and after four weeks of delivery, only 3 of them had had RLS symptoms with severity and sleep disturbances. IRLSSG criteria to assess RLS in pregnant women were defined already as diagnostic guidelines. Based on that Criteria 2 studies were conducted to assure the RLS symptoms in Pregnant Females. The first study was conducted in Italy a with 606 women at the time of delivery and second study was conducted in Brazil upon 524 women. Symptoms were assessed as double blind study using the IRLSSG criteria of 1995 for RLS. In that conclusion of Italian Female Study, 26.6% was found to be having RLS like symptoms and 62.7% of these women had never experienced RLS symptoms before pregnancy [14]. Prevalence was decreased up to 13% in pregnant women followed months. Few months later i.e. of 6 months only 7 Italian Females had reported to be have RLS like symptoms. Another study which was conducted in 524 Brazilian Females using the IRLSSG criteria of 2003 had shown 13.5% of prevalence in RLS and 94.4% were found to be affected in the 2nd or 3rd trimester with RLS like Symptoms. In that study, prevalence of RLS like symptoms or RLS was found to be 5.3%, 14.7% 15.2% in the first, second and third trimester respectively. From the study it was concluded and observed that the total prevalence or RLS like symptoms are found to be increasing by the progression of trimester in females during their pregnancy [15]. The results indicated that women who are having had primary or idiopathic RLS or RLS like symptoms during their pregnancy had a 4-fold increased risk of developing chronic RLS by the progression of pregnancy and life. Many Clinical trial studies have shown that there is increased risk of RLS developing with progression of age. In controversy, few studies have also reported rapid progression up to 70 years of age and then decreased or fixed stage of progression of RLS. Idiopathic RLS have shown rapid progression of disease up to 30-40 years of age in few clinical studies [16].

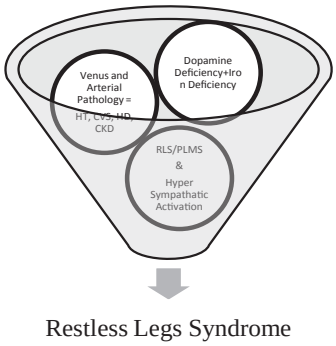

Figure 1A: Factors involved in pathophysiology of Restless Legs Syndrome.

The Indian perspective

RLS is a neglected diagnosis in India [17]. Due to absence of literature based on research done on RLS the exact prevalence is unknown. Mostly, the laboratory diagnosis leads to the iron deficiency and pain like symptoms in pregnant women. Due to non identical stage, RLS is a neglected diagnosis among Neurophysician and Gynecologists. Most of the time silent RLS or RLS like symptoms just treated with multivitamins and iron supplements [18]. The prevalence of RLS has been reported to be 1.5-6.6% in patients of medical renal disease as compared to the healthy humans. The Ratio of iron deficiency affected RLS is little higher than any other associated systemic disease. Females are more prone to RLS as compared to the males in Indian population in hospital based studies [19-21].

Etiology

Etiology or Causes of RLS depends upon various factors affected and classified accordingly. RLS if happen before 45 year or early stage of life can be primary (idiopathic) and after 45 years of age with any systemic disease called as secondary RLS. Individuals associated with iron-deficiency or anemia like conditions including pregnancy, renal failure, and anemia are more prone to develop Restless legs syndrome or like symptoms (Figure 1A). George Albert, et al. suggested that 34% of people who have iron deficiency or blood disorders have higher chances to develop RLS [22]. It is observed in Clinical surveys that if there is an association of systemic diseases with restless legs syndrome like Celiac disease, Auto Immune disease, Parkinson's disease, Thyroid disease and other illness like folate deficiency, magnesium deficiency, fibromyalgia, sleep apnea, uremia, diabetes, peripheral neuropathies, periodic limb movement disorder, vein disease can worsen the symptoms of RLS which affects the quality of life more significantly [23]. If there is a dopamine dysfunction associated with neurological disease like ADHD can more worsen the stage of Restless legs syndrome [24-27]. Genetic Research focused on Genes showed the association of RLS and 5 Genes: MEIS1, BTBD9, MAP2K5, SKOR1, and PTPRD. PTPRD has shown strong correlation with Restless legs syndrome. Chromosome 6p21.2 which

shows the expression of gene BTBD9 has implicated association of Restless legs syndrome, Periodic limb movements. There are many loci found associated with restless legs syndrome but there is no exact role identified of that loci associated with pathology [6].

Pathophysiology

The pathophysiology of RLS is still a questionnaire and unsolved. Decreased iron levels in brain are associated with the down regulation and rate limiting step of dopamine precursor (Tyrosine hydroxylase) in substantial Niagara space [28]. Nigrostriatal dopaminergic system found to be more involved in the pathology of RLS and PLMS in most of the cases. Iron deprived rats with less iron levels in brain found to have decreased Dopamine1 and Dopamine 2 receptors which are associated with sensory and motor functions in brain. Reduced DAT, and increased extra-cellular dopamine in the striatum and a more consistent decrease in H- than L-ferritin in brain regions were observed. As noted above, two imaging studies of RLS patients suggest a possible decrease in the D2R binding, which could reflect a decrease in the D2 receptors, increase in extra-cellular dopamine, or both [22]. The autopsy studies have also shown a greater decrease in H- than L-ferritin. The role of iron in deficiency in the pathology of periodic limb movements and Restless legs syndrome has been established via various clinical trials [23]. In many cases radio diagnosis like CT scan, MRI, Autopsy of brain, have shown lower iron levels in substantia nigra which is evidence for PLMS and RLS pathology [28]. Decreased cerebro spinal fluid ferritin levels in RLS patients are observed which are associated with decreased iron levels in blood and cerebrum. In 1982, by accidental study l-dopa was found to be effective in decreasing the RLS symptoms, moreover patients who have late onset of action of RLS are less iron producing than early onset of RLS [22-29]. Since 1982, l-dopa and other dopaminergic agonist are in use for the treatment of RLS and PLM. The successful treatment with iron and L-dopa state that dopamine have possible significant role in treatment of pathophysiology of restless legs syndrome [30]. Combined therapy of peripheral dopaminergic agonist domperidone when used with l-dopa, did not decrease the threshold of pergolide (a dopamine agonist) in treating RLS. This study supports one hypothesis that central dopaminergic systems play a major role in pathology of RLS than peripheral dopaminergic system. Hence, dysfunction in the central processing of sensory stimuli defects D2 binding in the medial thalamus and anterior cingulate gyrus which are mainly involved in central sensory processing. The diencephalon-spinal dopaminergic tract via medial pons has shown so much attention as the potential anatomic site of dopaminergic dysfunction in RLS (Figure 1C). According to the Clemens and Hatchman, the possible brain mechanistic pathology is Hypothetical spinal cord positive feedback mechanism mediating dopamine responsive Restless Legs Syndrome shown in Table 1. Shows that dopamine agonist which inhibits preganglionic sympathetic nervous system, hence basal sympathetic tone may increase. Increased adrenaline level via innervations of skeletal muscle, in reaction, it might irritate muscle spindles. The resulting enhanced input from pain-encoding high threshold muscle

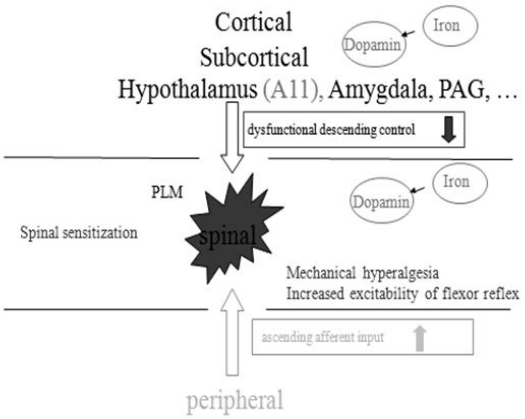

Figure 1B: Possible pathophysiology of restless legs syndrome.

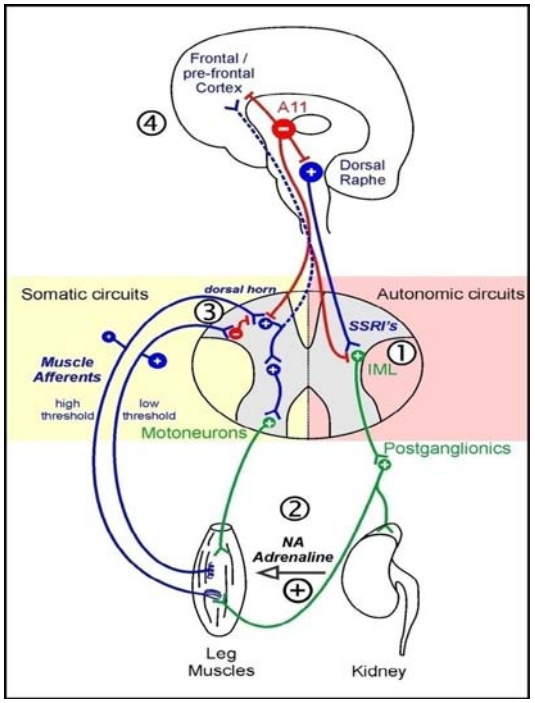

Figure1C: Possible Pathophysiology of RLS [53].

afferents in lamina I are insufficiently suppressed in the absence of DA or D2-like receptors. Dopaminergic system and its involvement in the sensory cortex, spinal cord and limbic system including all sleep pathways indicates and explains the possible involvements of circadian pattern of symptoms in Restless legs syndrome. Brain iron or ferric levels deficiency associated with RLS, and iron therapy found to be effective and curative in most of the cases [30]. Earley, et al. had stated that decreased levels of cerebrospinal fluid, ferritin and increased transferrin levels in restless legs patients when compared with normal control patient's Cerebrospinal fluid levels ferritin levels

Table 1: Hypothetical spinal cord positive feedback mechanism mediating dopamine responsive Restless Legs Syndrome [54].

1) Dopamine Agonist inhibits preganglionic sympathetic, Hence, basal sympathetic tone may increase.
2) Increased adrenaline level via innervations of skeletal muscle, in reaction, it might irritate muscle spindles.
3) The resulting enhanced input from pain-encoding high threshold muscle afferents in lamina I are insufficiently suppressed in the absence of DA or D2-like receptors

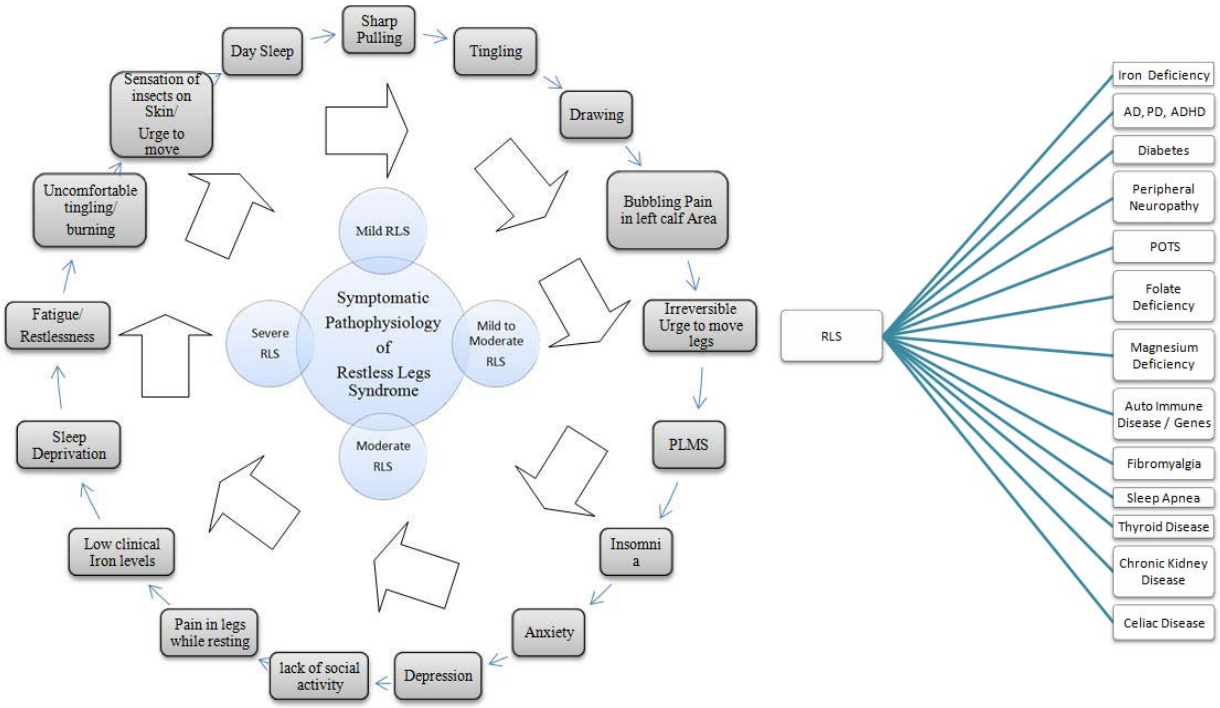

Figure 2: Clinical sign and symptoms of restless legs syndrome.

and transferrin levels, there was no any significant difference in serum ferritin levels [31,2]. It showed the controversy of iron and possible dopamine involvement in RLS pathology [31]. In iron deficiency or anemia/megaloblastic anemia, defective iron metabolism in the brain could be the major cause responsible for RLS in pregnant women. A huge number of patients were being observed with MRI were found decreased regional brain iron concentration in primary RLS patients as compared to the normal subjects. Depending on the observation stated and derived hypothesis conclude that transferrin receptors are decreased and iron regulatory protein1 (IRP1) is deficient (Figure 1B). Various significant biochemical links has been discovered between dopaminergic system and brain iron metabolism system associated with developmental RLS either primary or secondary. Iron plays an important role in the synthesis of tyrosine hydroxylase which plays an important role as rate limiting enzyme in the production of dopamine in brain. Therefore, the dopamine transporter system (DAT) is malfunctioning during iron deficiency [30]. Significant improvement of RLS symptoms has been checked and proven with combined therapy of iron and oral opioids [16]. Hammers A, et al. have found negative correlation with RLS severity and 11C-diprenorphine uptake in the caudate nuclei, medial thalami and anterior cingulate gyri, although pathophysiological significance of this finding is not clear [16].

Signs and symptoms

Patients with restlessness have the urge to move, and uncomfortable sensations, mood confusion and depression like symptoms require potential medical treatment with specific differential diagnosis. RLS presents a wide range of symptoms like unpleasant sensations in the legs, including burning, tugging, tightening, and feels "like insects crawling inside the legs", which are mostly sensorial. Symptoms of Restless legs syndrome are not all time painful but stressful and confusing as patient can't explain what had happened with him at night and why he was unable to sleep [32]. Generally, patients with restless legs syndrome feels uncomfortable and deep sensations within the leg rather than on the surface like something is walking inside. Restless legs syndrome symptoms also involve other body parts affected. With the progression of the disease the symptoms vary within other parts of the body and more worsen with the passage of time and as disease progress. Rest or inactivity such as lying or sitting initiates or worsens the unpleasant sensations. More restful the position and longer the duration, more likely is that the symptoms will occur. Minimal number of patients associated with restless legs syndrome who feels periodic limbs movements and motor symptoms like dyskinesia. These patients usually do not complain about RLS but complaint about the motor symptoms and body pain hence the diagnosis go confused with dyskinesia and Parkinsonism like syndromes. Motor manifestations are the justification of slowing of cerebral cortical activity according to the most of the animal

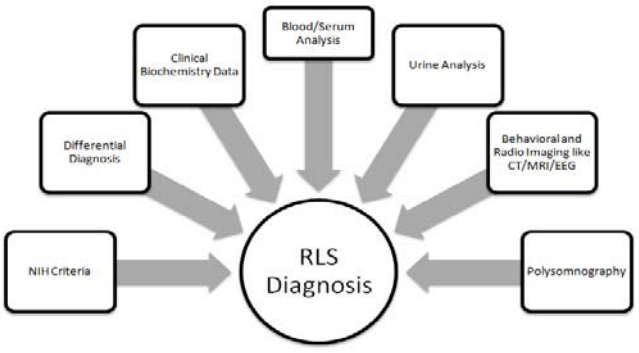

Figure 3: Clinical diagnostic tools of restless legs syndrome.

studies and clinical trials done with the patients of RLS. As the severity of RLS increases, more and continuous movements provide progressively less relief. However, individual suffering from severe stage of restless legs syndrome regularly develop symptoms with variant intensity throughout the day. Trademark of this syndrome is symptoms usually get worsen at the evening or night [2]. With the help of EEG of brain along with polysomnograph one can determine the sleep cycle disturbance and leg movements. In many studies it has been indicated that the peak in restlessness occurs in few time i.e in thehours immediately after midnight [32](Figure 2).

Diagnosis

Clinical diagnosis: RLS is certainly, a silent killer, very common but undiagnosed, require sufficient clinical and non clinical data to identify it on early stage [18]. RLS is very common in Women rather than man with 2:1 ratio. RLS require more research to establish the perfect pathophysiology and bio markers. Early diagnosis can make a difference in treatment [2]. International RLS study group (IRLSSG) has established the essential criteria for the critical diagnosis of RLS. Four essential criteria are required to make the diagnosis of RLS. These include: [1] distressing urge to move the limbs because of paraesthesia or spontaneous jerks in the legs or less often in other body parts; [2] worsening of these symptoms at rest; [3] temporary relief by motor activity; and [4] worsening of the symptoms in the evening or during the night. Essential diagnosis is made by total deep family history with RLS, effective centrally acting dopamine agonist agent treatment, and periodic leg movements at midnight. Generally early onset of the restless legs easily goes away when exercise or walk or with iron/dopamine therapy but it progress with the age and worsen at later stage [6]. At this time medical attention is required for routine iron status, should be routinely evaluated because decreased iron stores are a potential risk factor that can easily be treated. The presence of peripheral neuropathy and radiculopathy should also be determined (Figure 3).

Laboratory diagnosis: Laboratory Medicine is an essential diagnosis in this kind of particular diseases which is common but undiagnosed [18]. For the identification of Restless legs syndrome it is important to check out the serum iron levels and general anaemia biomarkers like RBC count, hemoglobin level in blood, and haematocrit. According to the diagnostic criteria, the normal iron level for adults is 20-300 µg/L for men and 20-150 µg/L for women [31]. Periodic limb movements are the essential diagnosis for RLS. According to the guidelines, the number of periodic leg movements per hour of sleep (PLMS-index) has often been used as an objective measure for severity of RLS and values above 5/hour are considered abnormal. As per research done so far patients with below 60 years of age and having narcolepsy, sleep disorder, insomnia, periodic limb movement disorder like disorders also show 5/hour limb movements which confuses with the RLS diagnosis. In such patients polysomnography and EEG recording along with blood serum iron levels become essential key criteria for the diagnosis [33,34].

Differential diagnosis: RLS is still not as much clearly identified well hence the diagnosis among the patient of RLS is poor. Most of the time it is neglected diagnosis [17,18]. The sign and symptoms are varying at the progression of stage and that is why more often misdiagnosed among few movement disorders. Most of the times neurologists and general physicians get confused between akathisia, Periodic limb movement disorder and nocturnal leg cramps. Few of the systemic disease like peripheral artery disease and arthritis make confusion in diagnosis as they can also produce the same pain and leg movements with pain [35]. Most of the time pregnant women, who develop RLS with low iron levels are maltreated as iron and multivitamin tablets by the gynecologists and physicians. Due to lack of awareness of this disease, it is most of the time neglected diagnosis. The differential diagnosis is required to stop progressing of the restless legs syndrome [34].

Treatment

Treatment of RLS includes so many things varying with diagnosis, symptoms and the stage of RLS progression. Qualified sleep physician may recommend lifestyle changes, medications or a combination to manage restless legs syndrome as it is mainly sleep disorder. The therapeutic treatment of RLS is limited with the data available on pharmacological therapy. Treatment include the exercise, stress reduction, changing daily habits like quitting smoking, using less coffee in drink, using less or no CNS stimulant, HOT water bath to reduce leg cramps. Medication of class Anti Parkinson, Anti Epileptic, and sleeping pills prescribed with and under guidance of consultant physician will be very helpful to gain normal sleep. If laboratory results shows the deficiency of iron or if any type of presence of anemia is diagnosed the iron pills with under guidance of physician will be very helpful to avoid neurological and physiological symptoms of restless legs syndrome. The treatment of RLS is symptomatic and not curative. One of the goals of therapy is to reduce the symptoms, their severity, and night-time awakenings. Medical management of RLS patients includes improving the overall quality of life. These desired targets can be achieved through therapeutic drug therapy, Physical exercise including life style changes and in few cases both together approached [16,35,36].

Non pharmacological therapeutic approach: There is no any history of trials of non-pharmacologic therapies for restless legs syndrome. Sleep medicine experts and neuropsychiartists suggest hot baths, massage, stretching, and moderate exercise, good sleep hygiene, avoid alcohol, caffeine, and nicotine intake as it improves the symptoms. In the evening, to avoid the symptoms activities that alert the mind, such as crossword puzzles and video games reduce symptoms. In severe RLS mild Physiotherapy with muscle relaxants is given to reduce the leg cramps and panic movements more often. Non pharmacological therapies include lifestyle changes, diet changes, routine drinking beverage changes and change in drug medication accordingly with the supervision of sleep medicine expert or with family physician.

Pharmacological treatment approach: There is no exact therapy for RLS has been developed yet but within the few clinical trials and experience of patients with pharmacological compounds found to be effective in severe to moderate restless legs syndrome. Drug tolerance and drug-drug interaction is also observed in many patients with renal, lever and other systemic disease patients. For pharmacological treatment, dopaminergic agents, opioids, benzodiazepines, anticonvulsants, iron, adenosine, adrenergic drugs, magnesium supplements, iron supplements and others. Iron supplementation ferritin is recommended in the low normal range,

most sleep physician and medicine experts highly recommend iron supplementation if ferritin concentrations are below 50 μg/L. Iron supplementation has not been found to be effective in RLS patients who do not have frank iron deficiency. Dopaminergic agents are always being choosen as the first choice for RLS is levodopa. Levodopa along with other GABA-A agonist like beserazide or carbidopa (dopa decarboxylase inhibitors) is indicated for treatment in mild to moderate or developing RLS [2,37]. The dopa-decarboxylase component prevents the peripheral conversion of levodopa to dopamine hence more levodopa is available to cross the BBB. The starting dose of levodopa is 50-62.5 mg, and final dosage for the severe RLS ranges from 100-250 mg. Common adverse effects of levodopa are altered taste sensation, nausea, headache, and dry mouth [35]. There are no possible chances to develop dyskinesias with levodopa use in RLS because generally they are seen in Parkinson's disease as it is used in low doses. Two therapeutic problems that are unique to Restless legs syndrome: augmentation and rebound. Rebound is the classical sign of symptoms appears again as medication wears-off and is directly related to the T1/2 of the drug given for medication. This kind of phenomenon has been observed in 20-35% of patients taking levodopa. Dopamine agonists who are frequently used for Restless legs syndrome are: levodopa, carbidopa, piribedil, pergolide, pramipexole, and ropinirole [38,39]. Piribedil is a dopamine agonist, which has been used for the treatment of restlessness frequently. That interacts with nigrostriatal dopamine receptors, i.e., D2 and D3. Although, pramipexole has a better affinity for the D3-receptor than the D2-receptor. Benefits of these agents are their longer half-life than levodopa, eliminating which is the main therapeutic concern about the limited duration of effect through the sleeping period. Intensity of augmentation is much lower than dopamine of these agents that is why safe for use. Cabergoline and rotigotine have also been studied for RLS [16]. Ropinirole was the first pharmacological molecule which had received FDA-approved labeling for therapeutic use in RLS. The initial dose of ropinirole is 0.25 mg and ranges to 0.5-4.0 mg. It is having lesser gastrointestinal side-effects, adverse effects include headache (34.4%), nausea (31.3%), dizziness (18.8%), and somnolence (15.6%), Augmentation (12.5%) of patients treated with ropinirole. Oral pergolide has also been used. The starting dose is 0.025 mg and ranges in between 0.5-1.0 mg. Side effects of oral pergolide include lack of sleep, dyspepsia, vomiting, headache, and rhinitis, Augmentation in 15-27% of pergolide-treated patient in clinical trials. Piribedil was found to be effective in RLS treatment. Dosage of piribedil ranges from 25 to 350 mg. It is beneficial as any kind of augmentation like phenomenon has not been observed. Adverse effects of piribedil medication reported are like narcolepsy like sleepiness, mental confusion, epigastric pain, increased palpitation [40]. From the clinical trials, compared to the other drugs piribedil was found to be more effective and safe for the treatment of RLS hence suggested as the first line treatment. Oral anti-epileptic drugs like gabapentin, carbamazepine, and valproic acid which are GABA agonist checked for RLS treatment in Placebo trial studies [38]. All the three inhibit impulse transmission at the spinal cord level. Moreover, GABA may play a role in dopamine and serotonin release, which could affect RLS is a current area of RLS treatment option research [34]. Gabapentin which is a potent GABA-A, GABA-B agonist can be used in the severe RLS with polyneuropathy as a first choice. The initial dose of gabapentin is 300 mg and ranges to 1,500-3,000 mg, depending upon the severity of RLS. Carbamazepine which is benzodiazepine class of drug is also used for the RLS in some specific conditions including systemic disease. It is chloride channel opener and its initial dose is 50 mg and ranges to 100-400 mg depending upon the progression of disease. The most common adverse effects are sleepiness, dizziness, and exanthema. Valproic acid is often used in the dose of 300 mg and ranges in between 1,000-3,000 mg for the treatment of RLS. Although valproic acid has side effects but it is used in combined therapy along with psychiatry patient related to RLS. The adverse effects more commonly observed are increase in body weight, tremor, fatigue, and hair loss. Opioids and opioid-agonists other benzodiazepines which are sometime prescribed by the neurology physician depending upon the severity of symptoms to improve the sleep performance is zolpidem with initial dose 5.0 mg ranging to 10-20 mg depending on symptoms and severity of disease [35,41]. Zonisamide, Zaleplon is also a benzodiazepine used but due to its adverse effects like mild or moderate hangover all the day, night falls in old age people and habituation it is not a more common choice of prescription [35,42].

Alternative therapeutics and diagnostic advancements in restless legs syndrome: The role of iron and calcium is well established and important in clinical management of RLS. The role of vitamin D is also essential and important in healthy skeletal system. Restless legs syndrome is a musculoskeletal disorder and its co relation with vitamin D deficiency is well accepted [45]. Vitamin D depletion and neuropsychiatric disorders are studied and its correlation had been established in many clinical and pre clinical studies. Research data on Vitamin D and Neurological disorder linking, provided evidence that Calcitriol (1, 25-(OH) 2 D3) is involved in brain function, and the nuclear receptor for 1, 25-(OH) 2 D3 has been localized in neurons and glial cells [46]. 1, 25-(OH) 2 D3 has been reported to increase glutathione levels, suggesting that the hormone has a role in brain detoxification pathways [48,49]. Nakamura, et al. showed that decreased glutathione content may cause the selective death of dopaminergic neurons. Moreover, In an animal study done by Shinpo, et al. found that low doses of Calcitriol (1, 25-(OH) 2 D3) were able to protect mesencephalic dopaminergic neurons against toxicity induced by L-buthionine sulfoximine and 1-methyl-4-phenylpyridium ions, which was resulting cause of depletion of glutathione content [47]. Orme, et al. concluded that when vitamin D was added to the culture media showed a dose-responsive increase in numbers of rat primary dopaminergic neurons with up regulating the expression of glial cell derived neuronal factor [46]. Furthermore, Balaban, et al. observed that Calcitriol (25(OH) D) levels in patients with and without restless legs syndrome found statistically significant for lower serum 25(OH)D levels in female with having Restless legs syndrome [50]. Trans-cranial Magnetic Stimulation (TMS) is a very important tool now days for the study of sleep disorders. TMS is observed in patients with sleep disorders for the moderate to severe restlessness as it covers the changes in cortical limbic region of brain. TMS has become a very effective tool in understanding the pathophysiological changes in sleep disorders. A Clinical study done by Giuseppe Lanza, et al. stated that there are significant changes noted for the patients with Obstructive sleep apnea and Restless legs syndrome associated patients. They observed that the patients were having, higher resting motor threshold in patients with OSAS (Obstructive Sleep Apnea Syndrome) than Restless legs syndrome. Moreover, they found that the cortical silent period was similar between patients with OSAS and

Control Patients but was little shorter than patients with having apnea [51,52]. The cortical silent period (CSP) refers to an interruption of voluntary muscle contraction by transcranial stimulation of the contralateral motor cortex. So it's a significant tool for the diagnosis and interpretation of therapeutic remedy for sleep disorders to the clinicians.

There are no any specific animal models available which exactly mimic the same mechanism of restless legs syndrome hence the pathophysiology of this disease is poor and under discovery [43]. Due to lack of developed mechanisms, RLS is more treated with symptomatically only. No any proven diagnostic biomarkers are available for the early detection of the disease. RLS is hidden diagnosis only made proven when entered in vast worst stage or many a times remains undiagnosed or misdiagnosed with other neurodegenerative diseases like Parkinsonism and maltreated. RLS is not most commonly prescribed as one of the most frequently undiagnosed disease which is common but undercover. As due to unclear pathophysiology of the disease number of pharmacologically treatment options are there which makes it most complicated and lack of consensus about the ideal treatment of RLS. Dopamine agonists and antagonists have been frequently studied agents for treatment of RLS but they have been also found as the actual cause of RLS in underlying secondary disease like Parkinsonism and Dementia. Other Class of drugs which frequently in use for the treatments are: GABA Agonists, Iron, anticonvulsants, opioids, and benzodiazepines. Many a times seems that the first line treatment option to treat RLS patients are gabapentin, Levodopa, Pergolide, and pramipexole, but most of them have shown increased and severe side-effects; while opioids show tolerance, addiction and severe called augmentation. So it's still a questionnaire whether should it be used as choice drug or first line medications are still questionable. Few more emerging molecules like piribedil, has shown some good results in clinical trials with no augmentation is raised hope for as future medicine. Restlessness is caused by inhibited or reduced GABAnergic transmission in brain which includes the hyper regulation of excitatory neurotransmitters, AMPA, NMDA (N-Acetyl D- Aspartase) in various cortical region of brain like dorsal anterior cingulated cortex (ACC) which can be easily identified with MRI and repetitive TMS. H-reflex, QST, and CuSP support the hypothesis of spinal or supraspinal hyperexcitability in restless legs syndrome patients. Repetitive TMS (rTMS) and tDCS are emerging as promising tools to transiently modulate cortical-subcortical circuit excitability in various neurological disorders including sleep disorders which neuropathology and neurophysiology is still a mystery and under discovery [50,51]. TMS are the emerging tool that provides promising signs in diagnosing the neurophysiology and neuropathology of such sleep disorders including psychiatric illness through the investigation of neurotransmitter changes in the various regions of the brain. It is the advanced techniques of diagnostics for sleep associated neurological illness. Although, TMS is added feature for diagnosing the patients with sleep disorders with EEG, Polysomnography and MRI findings for Clinicians, TMS is having some limitations like it can be used as full tool only along with some diagnostic clinical manifestation with other brain imaging data supporting to the disease progression and it also require sound and skillful technical expertization for the clinical manifestation of the pathophysiology as TMS provides the whole brain cortical stimulation pathway response in place of particular region of cortical excitability. Sham Stimulation is also required for clinical manifestation of the acquired data along with the patient with sleep disorder and control patient or data of control patient which is all time not possible to obtain the same.

Conclusion

Restless legs syndrome is fully neurological disease but its dramatic symptoms with idiopathic cause makes it most complicated disease. Curative treatment is possible only if pathology is identified. The urge for deep research of the root cause of RLS pathology is still burning issue due to lack of perfect animal models which mimic RLS which is a big Pitfall.

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