Restless Legs Syndrome:
Diagnosis and Management

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Restless Legs syndrome (RLS)

- First described in a case report published by Sir Thomas Willis in the 17th century; recognised as a distinct clinical entity by Karl Ekbom in 1945
- Sensorimotor disorder characterised by intense **discomfort**, mainly in the legs , during the **evenings**, when **at rest**, produces an irresistible **urge to move** the legs; symptoms **relieved by movements**
- May be accompanied by periodic leg movements in sleep, perceived by bed partners as kicks that occur in cycles of 20- 40 seconds
- Important cause of chronic sleep disturbance and consequent negative impact on daytime functioning

Prevalence and incidence of RLS (ICSD- 3)

- Prevalence 5- 15 % in European and North American population studies; lower in Asian countries (ICSD-3); increases with age up to 60-70 years
- Clinically significant prevalence of RLS 2-3% in Europe and North America, lower in Asia
- Twice as high in women than men
- Paediatric prevalence 2-4% in UK/US and Turkish studies; moderate to severe 0.8-2.2%
- Incidence 0.8 to 2.2%

Criteria for RLS diagnosis- ICSD-3, based on IRLS study group consensus

A) Urge to move legs ,usually accompanied by or thought to be caused by uncomfortable and unpleasant sensation in the legs

B) Urge to move or the unpleasant sensation begins or worsens during periods of rest or inactivity such as lying or sitting

C) Urge to move or unpleasant sensation totally or partially relieved by movement, such as walking stretching, at least as long as the activity continues

D) Urge to move or unpleasant sensations occur exclusively or predominantly in the evenings or night

E) Condition not accounted for by symptoms of another medical or behavioural condition

RLS diagnostic criteria cont.

- *RLS clinically significant when :*

  The symptoms of RLS cause significant, distress or impairment in social, occupational, educational or other important areas of functioning by the impact on sleep, energy/vitality, daily activities, behaviour, cognition or mood

- Diagnosis of clinically significant RLS : 4 essential criteria + impairment
- Supportive features : increase in PLMS index, especially PLMS with arousals index, family history of RLS

RLS diagnostic criteria cont

- Urge to move the legs may occur without the uncomfortable sensation
- Arms or other parts of the body may be involved in addition to the legs in 21-57%
- 50% report their RLS sensation as painful
- When symptoms severe, relief by activity or worsening in the evening may not be noticeable but must have been previously present

Terms used to describe RLS

(from Chaudhuri, Odin and Olanna 2004)

- Electric shocks
- Tingling; pins and needles
- Water moving
- Grabbing
- Aching
- Insects crawling
- Throbbing pain
- Irresistible urge to move
- “Heeby-jeebies”, Elvis legs, crazy legs etc.

RLS cont…

- RLS symptoms usually present between 4pm and 4 am. Patients with severe RLS may not fall asleep until 4am

- Family history of RLS, PLMs, especially PLMS with arousals, PLMW and response to dopaminergic therapy, supportive for diagnosis of RLS

Specific consideration for diagnosing RLS in children

- Child describes RLS symptoms in own words
- Diagnostician should be aware of words children/adolescents use to describe RLS
- Language and cognitive development should determine the application of RLS diagnostic criteria rather than age
- **There should be significant impact on sleep, mood, cognition and function; in children impairment often manifest as impairments in cognitive and educational domains**
- **PLMD may precede the diagnosis of RLS in children**

Supporting features for diagnosis of RLS in Children

- PLMS >5 per hour
- Family History of RLS among first degree relatives
- Family history of PLMS>5 per hour
- Family history Of PLMD among first degree relatives

Periodic Leg Movements in Sleep(PLMS)

- PLMs Characterised by periodic episodes of repetitive, highly stereotyped limb movements that occur during sleep

- Occur more frequently in lower limbs, and involve extension of the big toe, often in combination with partial dorsiflexion of the ankle, the knee and sometimes the hip

- A cortical arousal may precede, coincide with or follow the limb movements ; autonomic arousals with PLMS associated with significant heart rate and blood pressure surges

PLMS scoring

- Duration 0.5-10secs (candidate leg movement; CLM); if bilateral 0.5-15secs)
- Amplitude of movement, minimum 8µV increase in EMG voltage above the resting EMG
- **Minimum 4 consecutive candidate leg movements needed to define PLMS ;**
- **Period length between each leg movements should be 10-90 seconds**
- Leg movements on 2 different legs separated by less than 5 seconds between movements, counted as single leg movement

PLMS cont…

- Occur stage N 1sleep, frequent in N2 , decrease in N3 and usually absent in REM
- Record from both tibialis anterior muscles; electrodes placed 2-3cms apart
- **PLMS recorded as index of total sleep time**; **PLMS with arousals index is number of PLMS associated with cortical arousals**
- Night to night variability in PLMS ; up to 5 days may need to be recorded using leg actigraphy which has been validated with PSG

Differentiate from other limb movements in sleep

Differentiate from:

- Alternating Leg Muscle activation (ALMA): 0.5-3Hz, discrete and alternating bursts of Leg muscle activity in series of 4 or more, usually 100-500msec duration
- Hypnogogic foot tremors: 0.3-4Hz EMG bursts of 4 or more , usually 250-1000msec duration
- Excessive fragmentary myoclonus: small twitch like movements , fingers, toes corner of mouth; at least 5 EMG potentials per minute , over at least 20mins of NREM sleep, of 150msec duration or more
- Hypnic jerks: 20-100msec in sleep wake transition
- Myoclonus: 50-150msec

Criteria for diagnosing PLMD- ICSD-3

- Polysomnography demonstrates PLMS
- Frequency > 5 per hour in children or >15per hour in adults
- PLMS cause clinically significant sleep disturbance or impairment in in mental, physical, social, occupational, behavioural or other important areas of functioning
- PLMS and symptoms not better explained by another current sleep disorder, medical or neurological or mental disorder (**PLMS with apnoeas and hypopneas should not be scored**)

PLMD diagnosis cont.

- PLMS index must be interpreted in the context of a patient's sleep disorder. There is overlap of PLMS index values between symptomatic and asymptomatic individuals; **if asymptomatic not Periodic Leg movements disorder (PLMD)**

- PLMS in patients complaining of insomnia or hypersomnia, can be recorded when these complaints are due to other causes, such as anxiety disorder or obstructive sleep apnoea or narcolepsy; **PLMS are common but PLMD rare**; essential to demonstrate cause and effect relationship

PLMD diagnosis cont…

- PLMD cannot be diagnosed in the context of RLS, narcolepsy, untreated obstructive sleep apnoea, REM sleep Behaviour Disorder; PLMS common in these disorders but sleep complaint more readily ascribed to the accompanying disorder
- Diagnosis of RLS takes precedence over that of PLMD, even though sleep disrupting PLMS are recorded; **PLMS recorded in 85-90% of RLS patients**
- PLMD can be diagnosed if certain that PLMS have been induced by medication; **drugs precipitating or aggravating PLMS include SSRIs, SNRIs and tricyclic antidepressants, lithium and dopamine receptor antagonists**

Other disorders with reported increase in PLMS

- Multi system atrophy
- Dopa-responsive dystonia
- Sleep related eating disorders
- Spinal cord injury
- End stage renal disease
- Congestive cardiac failure
- Parkinson
- Post traumatic stress
- Asperger syndrome
- Multiple sclerosis

Dopamine impairment and or diminished inhibition of central pattern generators for PLMS, proposed as common factors in various disorders of PLMS

Differential Diagnosis of RLS

- Positional discomfort from nerve compression
- Sleep starts (hypnic jerks)
- Neuroleptic induced akathisia associated with dopamine receptor antagonists
- Painful legs / moving toe, not associated with circadian pattern or urge to move
- Sleep related leg cramps
- Leg pains associated with arthritis, vascular problems, neuropathy, sports injury; some of these worse at night or relieved by movement

RLS : onset course

- Onset all ages from childhood to late adult life
- Mean age of onset for familial RLS –third or fourth decades; onset prior to age 21 in one third
- In women RLS may appear during pregnancy; may be limited to pregnancy or recur and become persistent later in life

Course:

Early onset slow progression in two third of patients ;remaining third stable or may even remit

Late onset –often rapid progression

- Symptoms fluctuate; remission can be for months or years followed by relapse

Clinical Symptoms in RLS+PLMS

- RLS symptoms can be disabling in wake affecting social functioning
- Contribute to insomnia-initiating and maintaining sleep
- Patients may complain of fatigue and tiredness and poor concentration
- Disturbed mood
- Complain of hypersomnia, though not severe

- **Parasomnias**

Periodic leg movements in sleep in children and ADHD

- Picchietti et al (1999) suggest 3-5% of school age children in the USA have ADHD, and 64% of ADHD have PLMS. Concluded that sleep disruption may be factor in clinical presentation of ADHD
- Children with high PLM index may have early onset Restless Legs Syndrome especially if family history of RLS
- Sleep disturbance may resolve with dopaminergic medication
- Low ferritin level in 71.8% of children in Simakajornboon et al's study; responded to iron replacement

Pathophysiology of RLS

- Complex and not yet well understood
- Predominantly disorder of Central Nervous system
- Genetic mechanisms
- Central dopamine hypothesis
- Disturbed iron hypothesis
- Opiate system abnormalities
- Role of the peripheral nervous system

Evidence for CNS disorder

- ? Subcortical origin of RLS / Contribution from spinal cord
- PLM in wake and sleep found in patients with spinal cord lesion
- Spinal cord generator facilitated by suppression or decrease of supraspinal inhibition
- Functional MRI showed leg related sensory complaints associated with thalamic and cerebellar activation, and PLMW with pontine and red nucleus activation

Disturbed Iron System Hypothesis

- Iron distribution in brain highest in dopaminergic regions-substantia nigra and striatum
- Iron cofactor for tyrosine hydroxylase , rate limiting step in dopamine production
- Iron component of Dopamine-2 receptors; iron deprivation in rats leads to reduction in post synaptic D-2 receptors
- Low brain iron may lead to exaggeration of circadian fluctuation in plasma iron and dopamine synthesis and RLS symptoms; iron levels have diurnal pattern with nadir in late evening and early night

Disturbance of dopamine system

- Postmortem histopathology and immunostaining for tyrosine hydroxylase the rate limiting enzyme for dopamine synthesis in substantia nigra , showed no difference in RLS patients vs controls

- Imaging studies of dopamine system failed to show dopamine dysfunction ; SPECT studies of pre and post synaptic dopamine receptor bindings have shown no difference or conflicting results; PET studies also conflicting results for caudate and putamen uptake of flurodopa

Disturbance of Dopamine system cont…

- Are negative results due to focus only on nigro-striatal system or timing of studies?
- Suggestion that principal dopaminergic pathology may be in the diancephalo-spinal pathway, originating from the hypothalamus A11 dopaminergic cell group
- Hypofunctioning of A11 pathway postulated in RLS as this pathway exerts potent modulatory action upon spinal network via D-2 like receptors, including D-3 receptor subtype (Clemens et al 2006)
- One lesion study showed interruption of this sole source of spinal dopamine lead to RLS like phenotype

Disturbance of opiate system

- Positive pharmacological response to opiates

- Von Spiczac et al 2005 with PET study evaluating receptor availability showed that binding was related to RLS severity in areas serving medial pain system, including thalamus, amygdala, caudate nucleus, anterior cingulate gyrus and orbitofrontal cortex.

- Hypothesis: increase binding of endogenous opiates to post synaptic receptors to compensate for discomfort in RLS

  or the increased binding is compensating for defective opiate or other

  receptors in RLS

Role of peripheral nervous system

- EMG / NC studies normal in RLS patients
- Nerve conduction abnormalities and small fibre neuropathy found in subset of patients with secondary RLS, mainly in late onset non familial RLS

RLS pathophysiology cont…

Genetics:

- 50% of RLS patients report positive family history
- Families with autosomal dominant pattern with high penetration rate, with anticipation in early onset RLS
- Monogenic cause for RLS not yet found; polygenic model better fit for later onset RLS
- Independent genome wide association (GWA) studies in diverse population in Northern Europe identified 6 different genes that may play a role; BTBD9,MEIS1,PTPRD,MAP2K5 , SKOR1 and TOX3 account for 50-80% of population attributable risk for RLS

Medical and neurological disorders associated with RLS/PLMS

RLS may be due to overlapping factors (Zoidis 2003) : genetic makeup

+ environmental and medical factors

- Diabetes
- Peripheral neuropathy
- Alcoholism
- Parkinson`s disease / spinal cord lesions/ spino-cerebellar ataxias, multiple sclerosis
- Kidney failure
- Rheumatoid Arthritis
- Thyroid disease
- Iron/vitamin deficiency
- Caffeine/ alcohol
- Medications
- Acromegaly

Severity of RLS

- Mild – symptoms only at bed time
- Moderately severe - symptoms from 6pm and an hour before bed time
- Severe - symptoms develop before 6pm

- Check serum ferritin level

Non pharmacological therapies that may help in mild RLS: lack of controlled studies

- Aerobic and resistance training exercise effective in one study
- Lower body resistance training and walking on a treadmill three times a day improved RLS in one study
- Pneumatic compression devices and other pressure devices
- Massage and hot baths

Management of RLS

Avoid:

- Caffeine, chocolate, monosodium glutamate
- Limit use of centrally acting stimulants like decongestants, nicotine, antihistamines, appetite suppressants
- Avoid antidepressants tricyclics, mirtazepine, SSRIs / SNRIs) **except bupropion and nefazodone**
- Avoid antipsychotics- olanzapine
- Avoid antihypertensives (Calcium blockers)
- Avoid antiemetics (metclopramide)
- Proton pump inhibitors- interfere with iron absorption
- Avoid nicotine

Evidence base for treatment of Restless Legs Syndrome : 3 publications

- The long term treatment of restless legs syndrome/Willis –Ekbom disease: evidence based guidelines and clinical consensus best practice guidance: A report from the **International Restless Legs Syndrome Study Group** –Garcia-Borreguero et al in Sleep Medicine 14 (2013) 675-618

- Restless Legs Syndrome: Clinical presentation and diagnosis and treatment- Subhashie Wijemanne, Joseph Jankovic in Sleep Medicine 16(2015) 678-690

- Practice guideline summary: Treatment of Restless Legs Syndrome in adults- report of the Guideline Development, Dissemination and Implementation **Subcommittee of the American Academy of Neuro**logy –Winkelman et al in Neurology 2016; 87:1-9

Dopamine Agonists

- Reduce primary symptoms of RLS and also PLMS, including pramipexole, ropinirole and Rotigotine patch, but no head to head study

- Long term studies raise concerns regarding loss of efficacy in 50%, and side effects including augmentation and impulse control *(pathological gambling , hypersexuality, compulsive shopping, binge eating)* in 6-17% ; patients and families should be warned and physician enquire of these behaviours ; symptoms usually resolve with dose reduction or discontinuation

- Cabergoline and pergolide ergot dopamine agonists effective for RLS/PLMS but no longer recommended

Rotigotine (patch)

- Therapeutic plasma level over 24hours
- Start with 1mg/24 hours; maximum recommended dose 3mg/24 hours
- Rate of augmentation less than other dopaminergic drugs (2.7%) after one year, but **not yet compared with slow release formulations**
- Side effects : application site skin reaction (22-58%), nausea, headache, fatigue

Levodopa

- Levodopa combined with decarboxylase inhibitor, for rapid relief in primary and secondary RLS
- Dose Carbedopa/Levodopa ½-1 tablet of 25/100mg; max 50/200mg /day
- High risk of tolerance, augmentation and late night/early morning rebound
- Consider for use sparingly for infrequent symptoms

Calcium channel alpha -2- delta ligands

- Do not cause augmentation or impulse control

Gabapentin (GABA analogue); binds with high affinity alpha-2 -delta subunit of voltage activated calcium channels; inhibits calcium current and reduces neurotransmitter release and post synaptic excitability

- Dose 600-2400mg; starting dose 300mg 2-3 hours before bed time or before symptom onset ; reduce dose in patients with renal impairment

- Short half life

- Side effects : dizziness, somnolence, peripheral oedema , weight gain, recent warning regarding respiratory depression

Calcium channel alpha -2- delta ligands cont

Gabapentin enacarbil

- Once daily dose
- Dose 600mg with food , usually around 5pm ; lower doses 300-450mg may be effective; 1200mg dose effective in **RLS symptoms + sleep disturbance**

Pregabalin –gabapentin analog

- Dose : 50mg three times a day; maximum 300mg a day
- One study 300mg dose more effective than 0.25mg pramipexole but not 0.5mg pramipexole
- Side effects – suicidal ideation, dizziness and somnolence , addiction

Opioids

- Low potency opioids (codeine, pentazocine, meperidine) and medium potency opioids (tramadol, hydrocodone), effective for intermittent mild RLS
- Can be combined with alpha-2-delta ligands
- Data on long term efficacy in one study; 20/36 continued treatment for average 5 years (1-23years); addiction and tolerance in 1/36; increase in sleep apnoea

Opioids cont…

- Prolonged release Oxycodone-naloxone effective short term treatment in severe RLS
- Methadone , a long acting opioid in 2 studies showed sustained benefit over 2-10 years
- **No augmentation except with tramadol**
- **Concerns regarding addiction and sleep apnoea limits use to refractory RLS patients**

Opioid doses

- Codeine 15-30mg/day ; max.120mg/day
- Hydrocodone 5-10mg/day; max. 20-30mg/day
- Methadone 5-10mg/day ; max.20-40mg/day

Iron therapy

- Oral iron if Ferritin level <75 microg/L; ferrous sulphate 325mg a day with 500mg vitamin C to aid absorption; can take 4-6 weeks to achieve goal of >50 microg/L; avoid overload
- IV iron beneficial in open label studies including in patients with normal ferritin levels
- Risk of anaphylaxis with IV iron Dextran, less risk with IV ferric carboxymaltose (500mg, 2 doses 5 days apart), low molecular weight dextran , iron sucrose and ferric gluconate
- Other side effects , nausea, cramps , bloating and headache

Benzodiazepines and other treatments

- Benzodiazepines- useful for insomnia associated with RLS, after psychological and behavioural interventions
- Temazepam 7.5-15mg/ day; max 30mg/day 0.25mg-2mg /day, clonazepam can be used sparingly
- Intrathecal morphine pump
- Deep brain stimulation of bilateral posteroventral lateral globus internus in one patient , positive response in one patient; indirect evidence that Gpi stimulation reduced RLS symptoms with variable response to stimulation of subthalamic nucleus in patients with Parkinsons disease or dystonia

Treatment of augmentation

- Progressive earlier onset of RLS, with gradual shift to onset early evening, afternoon or also morning, with increase intensity of symptoms; short latency after rest and symptoms involving upper limbs and trunk; shorter duration of effect of medication
- Distinguish from natural progression of disease
- Augmentation less with long acting preparations; low ferritin increase risk of augmentation
- Gradually withdraw dopamine agonist ; patient may need an opiate , IV iron or alpha-2 delta ligand during withdrawal of dopamine agonists
- Avoid re-introduction of dopamine agonist

Consensus treatments

First line treatment:

- Alpha-2-delta ligands for RLS patients with severe sleep disturbance, comorbid anxiety, comorbid pain or RLS with pain or previous history of impulse control disorder or anxiety
- Dopamine agonists for patients with severe symptoms, excessive weight, comorbid depression, increased risk of falls or cognitive impairment
- Alpha -2-delta ligands more likely to cause weight gain and somnolence; fluid retention and oedema more likely with dopamine agonists; concerns regarding daytime sleep attacks
- Significant daytime symptoms- consider long term preparations

Consensus treatments cont…

Second line treatment

- Combination treatment with dopamine agonists and alpha-2-delta ligand, or opioid like drugs (eg codeine, tramadol)
- Lack of evidence yet for IV iron, but some data on efficacy of IV carboxymaltose

Severe Refractory RLS

- Opiates such as methadone
- IV iron
- Combination therapy with opiates

Consensus treatments cont…

- RLS in Pregnancy – replenish iron stores prior to pregnancy. Try non drug treatment

- Childhood RLS- oral iron if ferritin low ; gabapentin, pregabalin; ?? Dopamine agonists

Conclusions

- Consider RLS +/-PLMS in all patients with complaint of sleep onset and maintenance insomnia
- RLS a clinical diagnosis using strict RLS criteria
- Sleep studies indicated with sleep complaint and impact on daytime functioning out of proportion to RLS symptoms or to exclude RLS+PLMS lowering arousal threshold for parasomnias
- Check ferritin level as first step; mild symptoms avoid regular medication
- Alpha 2 ligands/ dopamine agonists/opiates depending on severity
- Be aware of impulsive behaviours and augmentation with dopamine agonists