Restless legs syndrome

Restless legs (previously called Ekbom’s syndrome) is common and annoying (I speak from personal experience!). For some it is more severe and affects their quality of life and sleep, and it is these people we often see in the surgery. This clinical review in the BMJ helpfully outlines some of the issues to consider (Clinical Review BMJ 2012;344:e3056).

Clinical features

- The diagnosis is clinical.
- The typical features are:
  - Urge to move, usually but not exclusively in the legs, partly or briefly relieved by moving.
  - Often accompanied by abnormal sensations (burning, tingling, aching or ‘insects crawling under the skin’).
  - In some, pain is the main presenting feature which can lead to them being mis-diagnosed with other conditions.
  - Tends to be much more common in the evening.
  - 80% get periodic limb movements whilst asleep, which may wake them.
  - Usually worsens over time but often with periods of remission, especially in younger people.
  - Affects all ages, but more common in the elderly.
  - More common in women than men and very common in pregnancy (up to 25%) and tends to worsen as the pregnancy progresses.
  - Can be a minor annoyance or a major issue affecting quality of life if severe.

Differential diagnosis

- Peripheral neuropathy
- Cramp
- Akathisia (motor restlessness caused by neuroleptics) or other drug-induced dyskinesias
- Parkinson’s with sensory features
- Hypnic jerks (sudden jerking as you are about to drop off to sleep).
- Arthritis
- Fibromyalgia
- Varicose veins.

Causes

Lots of causes have been postulated, but the cause is still unclear.

<table>
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<th>Idiopathic</th>
<th>Secondary</th>
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<td>Seems to have a strong genetic component with 20–60% having a family history.</td>
<td>Iron deficiency (but don’t be reassured by normal haemoglobin: serum ferritin should be checked). Pregnancy/Uraemia/Neurological problems/Drugs</td>
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- Antipsychotics/Antidepressants (especially SSRIs & SNRIs)
- Antihistamines
- Dopamine receptor blockers (e.g. metoclopramide, prochlorperazine, diphenhydramine (Nytol, Benadryl))

- A systematic review has shown links to cardiovascular disease, diabetes, obesity and dyslipidaemia, but the nature of such associations are complex and probably interrelated.

Investigations

- Measure serum ferritin.
- Do not be reassured by a normal haemoglobin: you must check ferritin levels.
- If ferritin <112pmol/l (50mcg/l) start iron supplementation, even if haemoglobin normal.
Management

- Most do not need drug treatment, but all with a low ferritin (<112pmol/l or 50mcg/l) should be offered iron supplements, even if their haemoglobin is normal.
- Usual advice includes:
  - Avoiding alcohol, smoking, and caffeine.
  - Good sleep hygiene.
  - Moderate regular exercise, avoiding over-exercising.
  - Brief walks, leg massage and hot baths before bedtime.

Drug treatment (about 20% of people need drug treatment).

- Consider only if non-drug treatment and iron supplements do not improve symptoms.
- The licenced agents are all non-ergot derived dopamine agonists: ropinirole, pramipexole and rotigotine. There is insufficient evidence to recommend one over another. A Cochrane review showed that dopamine agonists improved severity, sleep quality and quality of life, but only moderately so. However, dopamine agonists are associated with a number of problems:
  - Augmentation of the disease (coming on earlier in the day, increased severity of symptoms, symptoms spreading to other parts of the body): particularly associated with higher doses so try to keep doses low. Low ferritin can also cause augmentation so if it occurs, check serum ferritin levels.
  - Rebound: don’t confuse augmentation with rebound – symptoms occurring in the early morning due to dropping plasma levels of the drug.
  - Impulse control disorders: pathological gambling, hypersexuality, compulsive eating. The BMJ clinical review suggests this affects up to 1 in 5 with restless legs on dopamine agonists. These are more common with higher doses, in women, and in those with a personal history of experimental drug use or a family history of gambling disorders. Ergot-derived dopamine agonists (bromocriptine, cabergoline, pergolide) are not recommended because of the risk of cardiac valve fibrosis.
- In the UK no other drugs are licenced for use in restless legs symptoms, but in 2007 the Movement Disorders Society reviewed the evidence and suggested:
  - Reasonable effectiveness for gabapentin (2 RCTs showing efficacy). In the US the FDA has just licenced a modified release pro-drug of gabapentin for use in restless leg syndrome.
  - A recent Pfizer sponsored RCT shows that pregabalin 300mg daily is as effective as 0.5mg pramipexole at reducing symptoms but showed lower (but not zero) rates of augmentation over 12 months (NEJM 2014;370:621-31). Pregabalin is of course significantly more expensive than gabapentin!
  - Some evidence for oxycodone, carbamazepine, valproate and clonidine.

The European Restless Leg Syndrome Study Group recommends dopamine agonists first line and reserves codeine, tramadol, gabapentin, as second line therapy (although note this use will be off-label use) although this is based on consensus of experts where evidence is not available.

Restless legs syndrome

- Diagnosis is clinical. Check ferritin and offer iron even if haemoglobin is normal.
- For most, understanding the condition, advice and lifestyle modification is sufficient.
- About 1 in 5 will need drug therapy. Non-ergot derived dopamine agonist are the only licenced treatment. Other therapies are recommended by the European Restless Leg Syndrome Study Group but this is based mainly on consensus and all are off-label.
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