

Nondrug-related aspect of treating Ekbom disease, formerly known as restless legs syndrome

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Abstract: Ekbom disease (EKD), formerly known as restless legs syndrome (RLS) has affected and bothered many people over the centuries. It is one of the most prevalent neurological disorders in Europe and North-America, affecting about 10% of the population. The main characteristics are the strong urge to move, accompanied or caused by uncomfortable, sometimes even distressing, paresthesia of the legs, described as a “creeping, tugging, pulling” feeling. The symptoms often become worse as the day progresses, leading to sleep disturbances or sleep deprivation, which leads to decreased alertness and daytime functions. Numerous studies have been conducted assessing the efficacy of dopaminergic drugs, opioids, and other pharmacologic agents in alleviating EKD symptoms. However, there is also a growing body of evidence demonstrating the effectiveness of nonpharmacologic treatments including life style changes, physical activity programs, pneumatic compression, massage, near-infrared light therapy, and complementary therapies. The working mechanisms behind these alternatives are diverse. Some increase blood flow to the legs, therefore reducing tissue hypoxia; some introduce an afferent counter stimulus to the cortex and with that “close the gate” for aberrant nerve stimulations; some increase dopamine and nitric oxide and therefore augment bio-available neurotransmitters; and some generate endorphins producing an analgesic effect. The advantages of these treatments compared with pharmacologic agents include less or no side effects, no danger of augmentation, and less cost.

Keywords: RLS, modalities, massage, intermittent compression, NIR

Introduction

Restless legs syndrome (RLS) has affected and bothered many people over the centuries.¹ In 1685, patients with RLS were first described as suffering as if going through torture.² It took another 260 years before the first detailed description of the medical traits of RLS was published.² Shortly thereafter, in 1960, Ekbom defined all clinical features and coined the term restless legs syndrome.¹ In his honor, the name of this pathology was recently changed to Ekbom disease (EKD). EKD is one of the most prevalent neurological disorders in Europe and North-America, affecting about 10% of the population, with women being afflicted almost twice as often as men.^{3,4} The usual presentation of this condition is characterized by a strong urge to move, accompanied or caused by uncomfortable, or even distressing paresthesia of the legs, described as a “creeping, tugging, pulling” feeling.¹ The symptoms often become worse as the day progresses, leading to sleep disturbances or sleep deprivation, which further result in impairment of alertness and daytime functions.⁵

Ekbom disease is generally classified as “primary” (genetic or idiopathic) or “secondary” (related to other medial or neurological disorders) or it can arise from

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a combination of factors.⁶ The treatment for secondary EKD is aimed mostly at dealing with the underlying conditions. For example, low serum iron levels are associated with EKD,^{1,7-9} and it has been shown that administration of iron can decrease EKD symptoms.¹⁰ Other pathologies such as diabetes mellitus, end stage renal disease, vitamin B12 deficiency, folate deficiency,⁹ Parkinson's disease,¹¹ uremia, and fibromyalgia¹² have been associated with EKD. The options discussed in this paper will be most beneficial for the treatment of primary EKD.

The diagnosis is based primarily on the complaints of the patient, as there are no biomarkers, classic measurable clinical findings, conclusive blood assays, or radiological and sleep studies that can clearly implicate EKD. A long-needed, standardized way to identify and substantiate EKD was developed by the International Restless Legs Syndrome Study Group (IRLSSG).¹³ It is a four-question survey that explores 1) whether the subjects have an urge to move their legs, 2) whether the symptoms begin or worsen during periods of inactivity, 3) whether the urge to move is at least partially relieved by movement, and 4) whether this urge to move is worse in the evening or night.¹³ Affirmative answers to all four questions means that the criteria for EKD diagnosis are met. The IRLSSG also defined three supportive features; they are: family history, presence of periodic limb movement, and the response to dopaminergic treatment.¹³ While they are not essential to the diagnosis of EKD, their presence can help resolve diagnostic ambiguity.

Diagnosis and evaluation of EKD

Different tools are available that measure severity of the symptoms and their impact on a person's life and track a person's progress or decline: the IRLSSG rating scale, Johns Hopkins RLS severity scale, RLS quality of life instrument, Epworth sleepiness scale, and the fatigue visual analog scale.¹⁴ The IRLSSG rating scale¹⁵ is a 10-question scale, developed by the IRLSSG as a means of assessing the severity of EKD and of tracking changes in symptoms associated with this pathology.¹⁵ It assesses the impact of EKD in a patient's quality of life and function. Each question can be answered with one of five possible answers with attached points (0–4) according to severity. Therefore, a maximal score of 40 can be obtained. Generally, an IRLSSG rating scale score between 1 and 10 corresponds to “mild”, 11–20 “moderate”, 21–30 “severe”, and 31–40 “very severe” EKD. The Johns Hopkins RLS severity scale was the first published clinical scale to assess EKD severity.¹⁶ It consists of only one item, which asks for the time of day the symptoms

start. Four possible answers are linked to scores as follows: 0 = no symptoms, 1 = bedtime-only symptoms (after or within an hour of going to bed), 2 = evening and bedtime symptoms (starting at or after 6 pm), and 3 = day and night symptoms (starting before 6 pm). This scale was mostly created for screening and epidemiological research.¹⁶ The RLS quality of life instrument¹⁷ consists of 17 questions assessing domains such as daily function, social function, sleep quality, and emotional wellbeing. For each question, the possible answers range from “never” to “very often”, with an attached score ranging from 5 to 1 respectively. The scores for the different domains are calculated separately. The Epworth sleepiness scale¹⁸ is used to determine the level of daytime sleepiness by giving the patient eight situations and asking for the chance of dozing off or falling asleep during those scenarios. The four possible answers are each linked to 0–3 points respectively. A score of 10 or more is considered “sleepy”, a score of 18 or more is considered “very sleepy”. The fatigue visual analog scale is a unidimensional fatigue measurement. Here the patient has to mark his/her level of experienced fatigue (during a determined time frame) on a 10-cm line. Its anchors are “no fatigue” on one side and “worst possible fatigue” on the other.

Pathogenesis

Compounding the fact that EKD has no measurable signs is the uncertainty about its patho-genesis. In the 1940s and 1950s it was assumed that EKD stemmed from vascular disturbances.² This theory came under disfavor when it was observed that patients with EKD responded well to dopaminergic agents, such as Levodopa, and dopamine agonists. Levodopa, a precursor of dopamine that can cross the blood–brain barrier and is metabolized in the brain into dopamine, is also used to treat Parkinson's disease, a low dopamine condition. It is this similar treatment response between Parkinson's disease and EKD that resulted in speculations that these two disorders might be related in their origins.¹⁹ Different hypotheses on EKD etiology – or lack thereof – prompt different treatment suggestions: the ones trying to manage the symptoms by changing the lifestyle, the ones tackling the peripheral nervous system and blood flow, and the ones addressing dopamine regulation in the central nervous system via pharmaceuticals.

Hundreds of articles exist on the treatment of EKD with pharmaceuticals. Many authors recommend exercises or other adjunct modalities for the treatment of EKD,^{6,12,20–27} but there are not many studies assessing the efficacy of

other treatments. I found: one systematic review assessing efficacy of acupuncture in the treatment of EKD;²⁸ three randomized controlled trials (RCTs) (one assessing a 12-week exercise program,²⁹ one assessing a pneumatic compression device worn daily,¹⁴ and one evaluating the efficacy of near-infrared [NIR] light treatment³⁰); three prospective interventional studies evaluating the efficacy of physical exercise,³¹ pneumatic compression device,³² and NIR light;³³ and three case reports assessing the effectiveness of massage therapy,³⁴ pneumatic compression device,³⁵ and NIR light.³⁶ All of these studies concluded that EKD symptoms significantly decreased after using these interventions. This article will focus on treatment options involving nonpharmacological alternatives (Figure 1). For most relevant research see Table 1.

Treatment options

Lifestyle

Lifestyle changes as an intervention for EKD include improving sleep quality by controlling sleep times and by reducing caffeine and alcohol consumption.^{6,7,29,37} Mental activity, such as reading, card games, or computer work, has been

suggested to be successful in decreasing EKD symptoms.³⁸ The success of these choices is not well documented.

Physical activity

Epidemiologic evidence indicates that lack of exercise is a strong predictor of and a significant risk factor for EKD.³⁹ Physical activity and exercise have long been the only nonpharmacological treatment options available to EKD sufferers. In fact, by definition, EKD is the urge to move that is at least partially relieved by movement.¹³ It was recently shown in a RCT that a 3-day per week exercise program of aerobic and lower-body resistance training significantly decreased EKD symptom severity.²⁹ While the authors did not attempt to explain the reasons for why or how exercise was successful in decreasing EKD severity, one can surmise that the increase in blood flow brought on by activity⁴⁰ could play a role. Shear forces between the inner wall of the endothelium and the moving blood stimulate the enzyme nitric oxide (NO) synthase.^{41,42} Once generated, NO diffuses into the smooth muscle of the endothelium and then quickly diffuses through the muscle tissue of the blood vessel. There it activates guanylate cyclase, which then activates the second messenger cGMP (cyclic guanosine monophosphate). Several steps follow and culminate in the relaxation of smooth muscles in the blood vessel. This leads to vasodilation and consequently to increased local blood flow.^{43–45} NO is also scavenged by hemoglobin in the blood.⁴⁶ Under low pO₂ (partial pressure of oxygen) conditions, during physiologic “hypoxia”, the red blood cells release NO to increase blood flow.⁴⁶ Another possible reason for the success of exercises in the treatment of EKD symptoms could be the exercise-induced release of endorphins.⁴⁷ Endorphins are endogenous opioid polypeptide compounds, produced by the pituitary gland and hypothalamus that produce analgesia and a sense of well-being.⁴⁸ Another central change occurring with exercise, and therefore a further potential mechanism with which physical activity can aid in decreasing EKD symptoms, is the increased release of dopamine.⁴⁹ It has been shown that especially during high-intensity exercise dopaminergic neurotransmission changes.⁴⁹ A study assessing the incidence of EKD during sleep following acute physical activity in spinal cord injury subjects⁴⁷ found a significant reduction in EKD as measured by polysomnographic sleep parameters and decrease of leg movements. The authors reject the hypothesis that dopamine deficiency could be involved in the symptoms felt by spinal cord-injured EKD sufferers because of their spinal cord trauma. Instead, they suggest

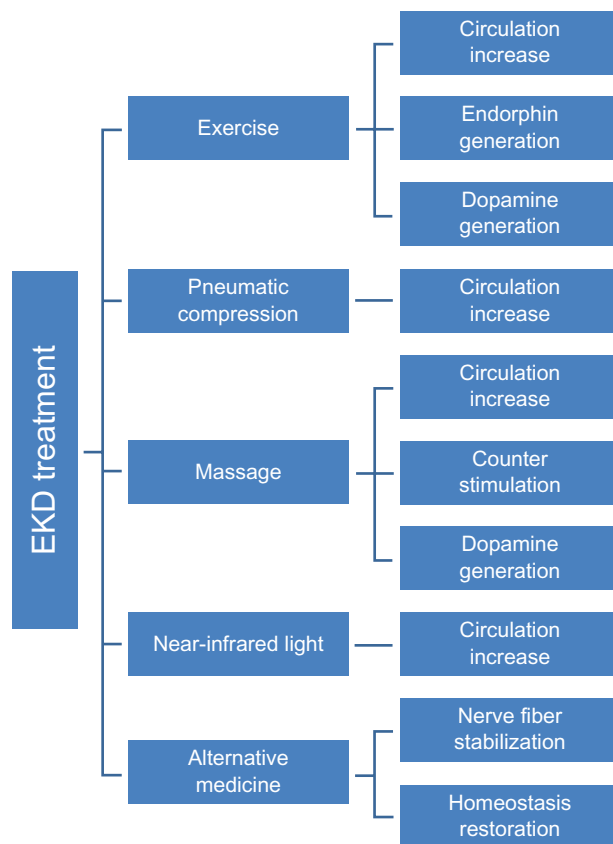


Figure 1 EKD treatment options and their potential working mechanisms.
Abbreviation: EKD, Ekbom disease.

Table I Most relevant research

| Treatment | Study | Study design | Number of patients in treatment group | Duration of study | Measurement tool |
|-------------|-------------------------------------|---|---------------------------------------|--------------------------|---|
| Exercise | Aukermann et al ²⁹ | Randomized, controlled | 11 | TIW for 12 weeks | IRLSSG scale |
| PCD | Lettieri and Eliasson ¹⁴ | Prospective, randomized, double blind, controlled | 21 | QD for 4 weeks | IRLSSG scale, JHRLS, RLS-QLI, ESS, Fatigue visual analog scale |
| | Eliasson and Lettieri ³² | Uncontrolled, prospective interventional | 9 | QD for 3 months | IRLSSG scale, RLS-QLI, ESS |
| Massage | Rajaram et al ³⁵ | Case series | 6 | QD for 35 days | IRLSSG scale |
| | Russel ³⁴ | Case report | 1 | BIW for 3 weeks | Functional rating index, digital symptom intensity scale |
| NIR | Mitchell et al ³⁰ | Randomized controlled | 17 | TIW for 4 weeks | IRLSSG scale |
| | Mitchell et al ³³ | Observational uncontrolled | 24 | TIW for 4 weeks | IRLSSG scale |
| Acupuncture | Mitchell ³⁶ | Case report | 1 | TIW for 4 weeks | IRLSSG scale |
| | Cui et al ²⁸ | Systematic review | Two studies with 120 and 48 patients | One treatment each study | "Ordinal outcome", VAS, longest and shortest duration of RLS symptoms in 1 month before and after treatment |

Abbreviations: BIW, twice per week; ESS, Epworth sleepiness scale; IRLSSG, International Restless Legs Syndrome Study Group; JHRLS, Johns Hopkins restless legs severity score; NIR, near-infrared light; PCD, pneumatic compression devices; QD, once per day; RLS-QLI, restless legs syndrome quality of life instrument; TIW, three times per week.

that the release of endorphins after physical activity may be the cause for the symptom reduction.

Pneumatic compression devices

One of the first modern-day (1940s and 1950s) hypothesis attempting to explain the etiology of EKD symptoms associated it with decreased blood flow.³⁵ Ekblom,¹ too, believed that vasodilators given to EKD sufferers would decrease the symptoms. The vascular hypothesis was later neglected but revived in 2005, when increased vascular blood flow with pulsed compression devices was shown to significantly decrease EKD symptoms in six patients.³⁵ Other studies have followed^{14,32} confirming these findings. The pneumatic compression devices were applied to the thigh and leg regions; the parameters used were 40 cm H₂O of air pressure intermittently for 1 hour. It is hypothesized that vascular compression stimulates the release of endothelial mediators (ie, NO)⁵⁰ that then can modulate EKD symptoms. It is also possible that intermittent compression, which enhances venous and lymphatic drainage, could relieve subclinical ischemia.¹⁴ These findings are not surprising, taking into account that a high prevalence (36%) of EKD in patients present with chronic venous disorder.⁵¹

Massage

Tactile and temperature stimulation, including massage or hot baths, can also be successful in decreasing symptoms

associated with EKD.^{38,52} While many authors mention these modalities as potential treatment options and numerous websites recommend them, there is a paucity of scientific trials confirming their efficacy. However, one case report³⁴ describes a 3-week massage regimen that decreased EKD symptoms significantly. This massage was given for 45 minutes twice a week using techniques such as Swedish massage (effleurage, petrissage), myofascial release, friction to tendinous attachments, stretches, and direct pressure to hip and lower extremity muscles. The symptoms returned after 2 weeks post treatment.³⁴ The author suggests that the natural release of dopamine following massage could have been responsible for the amelioration of the symptoms. Massage has shown to increase dopamine levels in urine by an average of 28% in different conditions.⁵³ Another speculation on the working mechanism of massage in the treatment of EKD is the counter stimulation it provides to the cerebral cortex. The tactile stimulation could supersede afferent input associated with EKD symptoms or at least partially modulate the perception of discomfort in the legs.⁵⁴ Another explanation involving the central nervous system is the possibility that tactile and temperature stimulations traveling in the spinothalamic tract may modulate neural activity in the thalamus. Bucher et al⁵⁵ have shown that activation of the thalamus is associated with sensory leg discomfort in idiopathic EKD patients. A fourth explanation could be the

mechanically induced increase of circulation. Massage moves venous blood to the heart, transporting nutrients to the tissue and metabolic products away from the tissue. Consequently, the potentially de-oxygenated tissue receives oxygen which then can restore vascular blood gas balance.

NIR light

NIR light has been used in the treatment of neuropathy to increase sensation and decrease pain,^{56–63} wound healing,^{64,65} and more recently in the treatment of EKD.^{30,33,36} The proposed mechanism of NIR light therapy is its ability to generate NO in the endothelium by activating the enzyme nitric oxide synthase (NOS)-3,⁶⁶ similar to exercise-induced NOS-3 activation. “Intensive illumination”, such as during NIR light treatment, can also free NO from hemoglobin and thus make it bio-available.⁶⁷ The discomfort that accompanies the EKD-related urge to move could be caused by the lack of tissue oxygen, which would be offset by an increase in blood flow. The urge to move may be a subconsciously driven mechanism to augment blood flow and tissue perfusion. Moving, such as walking or rubbing of legs,^{40,68} diminishes EKD symptoms as it enhances circulation. Therefore, treatment with a vasodilator, such as NIR-induced NO, could conceivably temporarily decrease the symptoms associated with EKD. Even a prolonged reduction of symptoms (up to a couple of weeks post treatment) has been observed.³⁰ This was explained with a potential systemic effect of light therapy.⁶⁹ This systemic effect could be responsible for either continued NO production or other changes in the tissue, leading to diminished symptoms. Additionally, NO has influence on neurotransmission.⁴⁴ It is one of the substances that influences nerve impulse transfer as it assists in converting nerve signals as they cross synapses.⁴⁴ This quality of NO might also be involved in reducing symptoms associated with EKD. All things considered, NIR could positively impact EKD symptoms by numerous methods.

Complementary and alternative medicine

The use of complementary and alternative medicine is another option available to EKD sufferers. Vitamins rank high on the list.⁷⁰ Their use in the treatment of EKD symptoms is based on the hypothesis that the unpleasant EKD sensations come from the stimulation of dysfunctional peripheral nerve fibers found along blood vessels.⁷¹ Vitamins E and B are associated with the nervous system. Intake of daily 300 mg vitamin E for 1 week may stabilize peripheral blood circulation and decrease symptoms.⁷¹

Vitamin B₁₂ intake may support the stability of nerve fibers, preventing excessive sensitivity and add further to the decrease of EKD symptoms.⁷¹ Multivitamins and vitamin C intake are also used to decrease EKD symptoms, followed by glucosamine, zinc, folic acid, vitamin D, and magnesium.⁷⁰ Nonbiologically based treatment options include prayer, meditation, and music.⁷⁰ Acupuncture is also considered an alternative medicine. It is an ancient Chinese medical therapy used in the prevention and treatment of disease.²⁸ It involves inserting needles into specific points on the body. A review article²⁸ studied several kinds of acupuncture methods, such as body acupuncture, auricular acupuncture, scalp acupuncture, electro-acupuncture, laser acupuncture, acupressure, and acupoint injection therapy for the treatment of EKD symptoms. The authors concluded that the evidence that acupuncture is an effective treatment option for EKD sufferers is still insufficient to support the hypothesis that acupuncture is more effective than no treatment or other therapies.

Placebo

As with all medication and treatment, the power of placebo must not be underestimated. The Latin word “placebo” means: “I shall please”, indicating a certain conscious expectation from a treatment. This means, that the context and environment of the treatment plays an important role in the patient’s improvement potential.⁷² A recent meta-analysis⁷³ assessing the placebo effect in EKD treatment studies found a considerable placebo response associated with EKD treatment. On average, more than one-third of EKD subjects experience a major improvement of EKD symptoms while receiving placebo treatment. The authors propose that the reason for this might be related to EKD’s unique responsiveness to dopaminergic agents and opioids – both systems implicated in the placebo response.

Conclusion

This article focused on treatment options for mainly primary EKD, involving nonpharmacological alternatives. Recommendations for patients with EKD suggest that certain life style changes, exercise, treatment modalities, as well as alternative medicine are linked to a decrease of symptoms associated with EKD. There is no research assessing the possibility of an enhanced effect of these modalities when applied together. It is very likely that the pathogenesis of this condition is multifaceted and therefore demands a comprehensive treatment approach. Because of the possible myriad side effects when treating EKD with

pharmaceuticals, the treatment options named above should be given consideration.

Disclosure

The author declares no conflict of interest.

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