**UNIVERSITY OF ZAGREB**
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# Secondary Restless Legs Syndrome


**GRADUATE THESIS**

**Zagreb 2020**

This graduate thesis was made at the Department of Neurology, Clinical Hospital Center, Zagreb, mentored by Prof.dr.sc Srđana Telarović, MD, PhD and was submitted for evaluation during the academic year 2020/2021.

**ABBREVIATIONS**

| | |
|---|---|
| RLS: | Restless legs syndrome |
| ID: | Iron deficiency |
| IRLSSG: | International restless legs syndrome study group |
| PLMS: | Periodic limb movements of sleep |
| CKD: | Chronic kidney disease |
| PD: | Parkinson's disease |
| WED: | Willis-Ekbom disease |
| SN: | Substantia Nigra |
| TIBC: | Total iron binding capacity |
| CNS: | Central nervous system |
| CSF: | Cerebral spinal fluid |
| DAT: | Dopamine transporter |
| RA: | Rheumatoid arthritis |
| CV: | Cardiovascular |
| RRT: | Renal replacement therapy |
| SDHD: | Short daily haemodialysis |
| NIH: | National institute of health |
| ICD: | International classifications of disease |
| SNP: | Single nucleotide polymorphism |
| QoL: | Quality of life |
| SNPC: | Substantia nigra pars compacta |
| IRP-1/2: | Iron regulatory protein 1/2 |
| TH: | Thyroid hormone |
| DBS: | Deep brain stimulation |
| DMT-1: | Divalent metal transporter 1 |
| SCA: | Spinal cerebral ataxia |
| HCG: | Human chorionic gonadotropin |
| TS: | Tourette syndrome. |

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## Abstract

**Secondary Restless Legs Syndrome**

**Ryan Murray Walker**

Secondary restless legs syndrome is now considered one of the most common disorders you have never heard of. With a prevalence of around 5 to 15%, this disorder affects a significant portion of the population and therefore requires attention. The objective of this review was to look at all of the possible secondary causes of restless legs syndrome and whether there is strong enough evidence to support these associations. It is now widely accepted that the first depiction of possible RLS was outlined in 1672 by the well-known English Physician Sir Thomas Willis. Restless legs syndrome diagnoses has to meet the criteria set out by the international restless legs syndrome study group (IRLSSG). Restless legs syndrome can present in many various forms and can occur at any time throughout life. Patients who suffer from restless legs syndrome will often experience motor and sensory symptoms, or one of the two components. There are also other associated features such as sleep disturbances and fatigue, that can often negatively affect the quality of life of the sufferer. Restless legs syndrome can be treated with various non-pharmacological and pharmacological options. In this review we found a strong association between restless legs syndrome and iron deficiency, renal disease and pregnancy. Parkinson's disease, essential tremor, some neuropathies and familial ataxias also showed some strong evidence towards an increase in the prevalence of restless legs syndrome in these disorders, however more long-term studies need to be done. We looked at many other possible associations, such as multiple sclerosis, myelinopathy, fibromyalgia and stroke. These, however, lack concrete findings to their associations, with possible alternative factors contributing to these associations with restless legs syndrome. It is important that restless legs syndrome sufferers be identified. Patients with mild symptoms, might simply need reassurance, while more moderate to severe symptoms might need pharmacological treatment. It is imperative that these secondary causes be screened when making the diagnosis of restless legs syndrome, as by treating them the symptoms of restless legs syndrome may be resolved and therefore not require other treatment modalities specific to restless legs syndrome.



Keywords; RLS, ID, pregnancy, CKD, PD, PLMS.

## Sažetak

**Sekundarni sindrom nemirnih nogu**

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u bilo kojem trenutku tijekom života. Pacijenti koji pate od sindroma nemirnih nogu često će imati motoričke i senzorne simptome, ili jednu od dvije komponente. Postoje i druge povezane značajke poput poremećaja spavanja i umora, koje često mogu negativno utjecati na kvalitetu života oboljelog. Sindrom nemirnih nogu može se liječiti raznim nefarmakološkim i farmakološkim mogućnostima. U ovom smo pregledu pronašli snažnu povezanost između sindroma nemirnih nogu i nedostatka željeza, bolesti bubrega i trudnoće. Parkinsonova bolest, esencijalni tremor, neke neuropatije i obiteljske ataksije također su pokazali neke snažne dokaze o Sekundarni sindrom nemirnih nogu sada se smatra jednim od najčešćih poremećaja za koji nikada niste čuli. S prevalencijom od oko 5 do 15%, ovaj poremećaj pogađa značajan dio populacije i zato zahtijeva pažnju. Cilj ovog pregleda bio je sagledati sve moguće sekundarne uzroke sindroma nemirnih nogu i postoje li dovoljno snažni dokazi koji podupiru ove asocijacije. Sada je široko prihvaćeno da je prvi prikaz mogućeg RLS-a izložio 1672. godine. poznati engleski liječnik Sir Thomas Willis. Dijagnoze sindroma nemirnih nogu moraju udovoljavati kriterijima koje je postavila međunarodna istraživačka skupina za sindrom nemirnih nogu (IRLSSG). Sindrom nemirnih nogu može se pojaviti na mnogo različitih načina i može se javiti povećanju prevalencije sindroma nemirnih nogu kod ovih poremećaja, međutim potrebno je napraviti dugoročnija ispitivanja. Pregledali smo mnoge druge moguće povezanosti, poput multiple skleroze, mijelinopatije, fibromialgije i moždanog udara. Njima, međutim, nedostaju konkretni nalazi o njihovim udrugama, a mogući alternativni čimbenici doprinose tim udruženjima sa sindromom nemirnih nogu. Važno je identificirati oboljele od sindroma nemirnih nogu. Pacijentima s blagim simptomima možda će jednostavno trebati osiguranje, dok umjerenim do težim simptomima može biti potrebno farmakološko liječenje. Ove sekundarne uzroke morat će se pregledati prilikom postavljanja dijagnoze sindroma nemirnih nogu, jer se njihovim liječenjem simptomi sindroma nemirnih nogu mogu riješiti i stoga ne zahtijevaju druge modalitete liječenja specifične za sindrom nemirnih nogu.



Ključne riječi; RLS,ID, Trudnoća, PB, KBB,PLMS

## Introduction and History of RLS

Restless legs syndrome (RLS) has been characterised by a few people as the 'most common disorder you have never heard of' (1). The name given to this syndrome, was initially described by Karl-Axel Ekbom, the renowned Neurosurgeon and Neurologist, from Sweden ((2). It is also important to note that in his work Ekbom outlined a sensory form, 'asthenica crurum paraesthetica' and, secondly, a painful form 'asthenia crurum dolorosa'. This division still stands true, in the 21st century. Interestingly, Ekbom further described that there was a link between anaemia and RLS, as well as pregnancy and RLS. He also mentioned the association between vitamin B12 deficiency and this syndrome. Nearly eighty years later, these associations still hold true in todays understanding of restless legs syndrome (2)

There is still some speculation around when this syndrome was first mentioned. Some may dispute that RLS was first discussed in age-old Chinese literature. A famous French philosopher by the name of Montaigne gave reference to RLS in his essay 'of experience', where he states 'from my infancy, that I had either folly or quicksilver in my feet, so much stirring and unsettledness there is in them, wherever they are placed'(1580). The Greek philosopher, Chrysippus was also known to have legs that used to move while at banquets(3). Other early mentions of this syndrome were by Boissier de Sauvages de la Croix in his work titled 'Nosologia Methodica', where he describes his findings in both men and woman, who in the evening cannot stop themselves from moving their legs, due to the constant feeling of restlessness. Later on Gilles de la Tourette(1898) described some features of RLS in his book titled 'Les Etats Neurasthenique'(4), where he refers to both the sensory feeling of 'prick' as well as a motor component 'toss and turn'. However, Gilles de la Tourette did not make reference to the fact that the unpleasant sensations in RLS seems to be worse at night in comparison to the day(5)

It is now widely accepted that the first depiction of possible RLS was outlined in 1672 by the well known English Physician Sir Thomas Willis. In a chapter of one of his works, he describes the contractions of ones limbs as well as the immense restlessness which leads to the hindrance of ones sleep. He goes as far as to perceive these features as torment 'the diseased are no more able to sleep, than if they were in the place of the greatest torture' (Willis, 1692). Interestingly, Sir Willis similarly gave mention to the association between RLS and iron deficiency

(Willis,1683). Furthermore, he described that there was a possible link to the involvement of the spinal cord and irritation thereof as a possible causative stimulus of this syndrome.

It is important to note that an essential component in RLS was observed in the 1960s. Coccagna and Lugaresi from Italy, were recording sleep in a polygraphic study of a patient who was complaining of leg movements and insomnia associated with these symptoms. They observed repetitive leg movements on the polygraph . It was also mentioned that there was a link to sleep and the onset of these movements. In 1975, Guilleminault and his co-workers, gave a name to these movements, calling them 'periodic leg movements of sleep'(6).It is important to note that PLMS today still plays an important role in the diagnosis and follow-up of treatment in RLS, and in research.

In 1995 a group was formed, known as the International Restless Legs Syndrome Study Group. This Group formulated criteria for the diagnosis of RLS, which, in turn, lead to a worldwide standard in diagnosing RLS as well leading to a worldwide standardised approach to the management of RLS patients (7). In 2003, the criteria were adapted by the National Institute of Health (NIH). In 2012, the criteria were further adapted.

The diagnosis of restless legs syndrome is made according to a symptomatology that adheres to five main criteria set out by the International Restless Legs Syndrome Study Group. They are as follows:

"1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.

2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.

3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.

5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioural condition (e.g., myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, habitual foot tapping).”

Over the past twenty years restless legs syndrome has become widely known as a commonly occurring disorder that is largely responsive to medications and various symptomatic treatment modalities. The IRLSSG rating scale was created back in the early 2000s. This questionnaire was further validated (8). This rating scale is still used today to determine the severity of this syndrome and to monitor symptom modification.

More recently The International Restless Legs Syndrome Study Group (IRLSSG) founded a committee to review the name of this syndrome. They decided that Willis-Ekbom Disease (WED) was a more appropriate name than Restless legs syndrome. However, in many circles today these names are used interchangeably.

## Epidemiology

By looking at the history of Restless Legs Syndrome, it is evident to say that RLS has a wide pattern of distribution on an ethnically, genetically and cultural level. Research studies with regards to epidemiologic prevalence has been performed in 5 of the 6 continents populated by humans. With the overall prevalence of RLS being stated at around 5-15% of the Caucasian populace, which seem to be the most affected, compared to other ethnic groups. RLS also seems to be twice as common in female's verses males (9) . Those of Northern European descent seem to have the highest prevalence. RLS and PLMs seem to show a cyclic day to day pattern, that is determined by several genetic elements, gender, age as well as by some medical diseases/disorders. RLS has a prevalence of 2% in the school going age group (10). The occurrence of this syndrome, increases with age with roughly 3% of those aged 30, to around 1 in 5 people over the age of 80 (11). RLS is observed in roughly 33% of pregnant woman during their third trimester. It is interesting to note that this percentage seems to increase in woman with multiple gestations (12).

Genetics also plays an important role in the epidemiology of RLS. Familial RLS has been recognised as an entity, showing autosomal dominant patterns of inheritance. A few susceptible gene loci associated to RLS have been found on a few different chromosomes (13).
RLS is a complex syndrome, influenced by several genetic factors instead of one individual factor. In 2007 there were two large scale research studies in genome sequencing that were presented. It was shown that in Icelandic and United states samples, there was a rather strong genome association with RLS and PLMS (14). The second study, showed that there was significant correlation between RLS and certain intragenic regions within a gene, found in French and German natives (15).

It is important to note that epidemiologically RLS often occurs as an idiopathic syndrome hence the term primary RLS. However, the prevalence that RLS is seen in some frequent medical settings transcends that of pure chance. These include iron deficiency, renal disease, diabetes and certain neurological disorders, to mention a few. These would be known as secondary RLS causes. Additionally, as common as RLS is and its wide epidemiologic distribution in various groups, it is still under recognised and therefore untreated by professionals. Therefore, it is important to increase the awareness of RLS.

## Signs and Symptomatology

RLS can present in many ways, with a vast array of symptoms which can diminish a patients' quality of life. These symptoms can hinder ones sleep pattern as well as affect social functioning on various levels. It is important to note that RLS typically presents with a broad array of motor and sensory symptoms. Beyond these common symptomatology, RLS can lead to fatigue, day time sleepiness, insomnia, lethargy, jitteriness as well as lack of concentration to mention a few (16).

The Symptoms of RLS can even occur at any age, even some presenting with RLS in childhood. The prevalence however increases with advancing age (17). The development of RLS is usually life long and progressive, with episodes of worsening symptoms over certain periods of time. It is interesting to point out, that RLS in some may present as paroxysms of 'acute attacks' with periods of absent symptomatology, which could potentially make the diagnosis more challenging.

With regards to diagnosing RLS, the IRLSSG, set out the 5 criteria mentioned earlier. This can be put to memory by the use of this acronym; URGES

**U**rge for one to change their leg position that can be accompanied by uncomfortable leg sensation.
**R**est usually triggers the onset of symptoms.
**G**etup and move usually relieves symptoms to some degree.
**E**vening as well as at the time of going to bed the symptoms worsen.
**S**olely not attributed to another medical disorder or another discernible condition.

Patients who suffer from RLS often will experience motor and sensory symptoms, or one of the two. Motor symptoms usually present with a compulsion to move a limb/s. This movement usually to some degree, relieves these uncomfortable sensations (18). Another important aspect of this disorder is that 80 to 85% of RLS patients start experiencing periodic limb movements (PLM). Periodic limb movements are described as stereotypical jerking movements that are repetitive in nature (19) They appear usually every 5 to 90 seconds. PLM can begin at times of sleep, known as periodic limb movements in sleep or it can occur during wakeful hours of the day, then referred to as Periodic limb movements awake (20).

It is crucial to make the distinction between the motor component of RLS and akathisia, which is an undesirable side effect to various neuroleptic medication. The sensory component of RLS consists of a multiple different features from dysethesias to cramping (21). Many patients have distinctive ways of describing their individual symptoms. Some referring to it as "electric shocks" to "itching bones"(22). Usually the lower limbs are the most common site affected, however the upper extremity, in particular the hand is also sometimes implicated (23) In most cases this affects both limbs.

Due to the nature of RLS, patients often suffer from sleep disturbances (11). Patients often complain of inability to fall asleep, poor quality as well as day time somnolence (24) It is important to mention that some pain is an important component of RLS. Almost two thirds of RLS patients suffered from varying degrees of pain. Fortunately, this pain can often be managed with specific medications. Augmentation and rebound symptoms can occur due to dopaminergic medication used to treat RLS. Over 80% of RLS sufferers using levodopa start to show signs of augmentation at some point- this is identified by symptoms beginning earlier during the day (25).

RLS symptoms can be debilitating and can have a huge impact on the quality of life of those suffering from the disorder. Up to 1 in 5 sufferers of RLS manifest with the severe form of the disorder(x), which leads to chronic sleep deprivation. This chronic sleep deprivation leads to further consequences for the patient such as depression. It can also cause a type of 'spousal arousal syndrome' where the partner who sleeps next to the RLS sufferer, also starts developing lack of sleep complications, due to the interruption of sleep by the movement of their partner (26) .

It is important to point out that RLS can occur in a chronic- persistent form, where the patient would experience symptoms at a minimum of 2 times a week, with the patient untreated. The Intermittent form usually would appear less than 2 times a week, when not treated, with RLS features occurring at a minimum of 5 times in the patient's life, in order for it to be diagnostic.

## Primary vs Secondary Classification

Primary Restless legs syndrome also known as idiopathic, has no other known cause hence why it is referred to as idiopathic RLS. In recent time primary RLS has be linked to certain genetic factors and can be considered in some, to be heritable (27). Primary RLS seems to affect a greater proportion of individuals compared to secondary RLS. The distinction made between primary vs secondary RLS, is that secondary RLS usually has an attributable cause.

The symptomatic presentation of both primary and secondary RLS are the same. However, one recent study showed that secondary RLS symptom presentation is harsher than in primary RLS (28). In this review we will focus on the secondary/identifiable causes of RLS.

## Iron Deficiency

Iron deficiency has shown to play a large role as a secondary cause of RLS. It is important to note that RLS usually only occurs once iron deficiency is established and usually is resolved once the condition is treated. It has been shown that increasing the bodies storage of iron in patients who suffer from RLS as well as are deficient in iron show a massive improvement in their RLS symptomatology, to even complete resolution of their symptoms. A conclusion has be drawn; disorders that decrease iron availability will subsequently lead to a higher possibility of developing RLS (29).

The bodies serum ferritin levels have widely been accepted as the best possible means to measuring iron status. A study was undertaken to measure bone marrow iron stores and compared this to serum ferritin measurements. Patients with a value of 45 micrograms per litre and below are considered to have low peripheral iron stores (30). It is important to also look at percentage of transferrin saturation as well as TIBC in ID associated RLS. Ferritin measurements at times are not always accurate, therefore it has been advised that values below 50 micrograms per litre should seek oral iron supplementation(31).

It has also be demonstrated that patients who suffer from RLS who later on develop ID, will show marked aggravation of their symptoms. A double blinded study was performed which recorded per oral iron supplementation. This study showed that RLS symptoms were significantly reduced, in those individuals who had documented low ferritin levels prior (32). It is crucial to point out that iron is the only substance that can definitively be displayed to cause RLS when its levels are significantly lowered as well as the correction of this iron deficiency, leads to complete resolution of RLS (29).

The concentrations of brain iron levels have also been studied. Iron levels vary in particular areas of the brain. These changes in iron status can also be seen in the ageing population (33). MRI was used to identify these specific regions in the brain, and to quantify these values in iron status. It is important to point out the connection between iron and dopamine. Various areas of the brain where dopamine generating areas have high iron concentrations were studied, more specifically the Substantia Nigra. Studies have shown that patients with earlier display of RLS symptoms (those before the age of 45 years)-considered early onset, have had markedly decreased iron concentrations within the SN (34). Another prominent observation was that these

iron concentrations measured amongst the study populations were inversely related to the clinical manifestation of their RLS(34)(35). Therefore those individuals with lower overall concentrations had a worse disease course, with an increased severity of symptoms. In a separate study ultrasound B-mode via transcranial methods was also performed to detect nigral-iron status. Noticeable areas of hypo echogenicity were detected within the SN indicating reduced iron stores in patients who had diagnosed RLS compared to the controls (36).

Cerebrospinal fluid investigation adds another dimension of CNS Iron status. A study performed in Japan as well as the United states both showed promising results. In comparison to their controls, both studies showed that sufferers of RLS had a decrease in CSF ferritin levels as well as an increase in CSF transferrin. Interestingly when the same patients with RLS and controls, had serum iron and transferrin measured, the results did not vary to be considered significant (37)(38). It is not only important to pay attention to the overall iron status, but also to focus on the daily variation of these values. In one of the studies this circadian fluctuation was detected by CSF values recorded in the evening, instead of in the morning.

In this evening sample it was noted that a significant drop in CSF ferritin was detected in RLS Patients, who in the group were considered early onset RLS suffers. In comparison to RLS suffers who were diagnosed as late onset, i.e., after the age of forty five, who had CSF ferritin levels recorded in these nightly samples, however they were not considered as significantly lower compared to the controls (39). This points out the necessity to study circadian changes in iron with regards to RLS and to look into how this varies in the different sub categories of RLS patients. Autopsies were also performed on patients with earlier onset RLS, which firmly established the link between brain iron deficiency. An array of various stain sections of the SN were performed. They all showed a decrease in iron as well as an increase in transferrin in comparison to the controls, further cementing the causal relationship between iron status and RLS (40).

Another observation was that transferrin receptor was diminished This is an interesting observation because the opposite should be expected. Usually in ID an increase should appear in transferrin receptor. The transferrin receptor is controlled by certain regulatory proteins, these being IRP1 and IRP2. To further understand their influence on this syndrome, they were studied using micro laser techniques, in order to separate neuromelanin cell types from the SN. The isolates of neuromelanin from the SN of RLS patients demonstrated to have an increase in

IRP2 however IRP1 was decreased in comparison to controls(41). This unanticipated decrease in IRP1 might give explanation as to why the transferrin receptor is decreased, which in states of ID should in fact be elevated. This decrease would possibly lead to the limitation of cellular iron availability, which in turn leads to brain ID. What we cannot yet conclude is whether this decrease in IRP1 is due the shortage of available iron, i.e. secondarily or is this decrease in IRP1, actually the true primary pathogenesis of RLS. It was also noted that patients with RLS, also had largely decreased iron transport proteins, this being DMT1 and ferroportin. In conclusion the earlier onset type of RLS appears to be due to aberrant iron modulation that is expected to cause the RLS symptoms rather than the other way round.

The iron dopamine causal relationship has also been extensively studied. The question that has arisen, is as to how does ID lead to these symptoms of RLS? It is also clear that variation in the dopaminergic system, also has an impact on the symptoms of RLS. This is seen by the use of dopaminergic medication in the treatment of RLS. The relationship between how iron affects the dopaminergic system has been investigated in several studies. Both in vitro and in vivo studies have been undertaken. In rat models that had deliberate dietary induced iron deficiency. These models showed decreased brain iron by one third to around half the values in comparison to the controls. An increase in transferrin and a decrease in ferritin values were also observed in these animal models (42). Interestingly when iron concentrations were measured in different areas of the brain, the decrease that was observed was not uniform throughout, but rather showed a diverse range of concentrations. The area where they detected the largest decline in brain iron concentration, was in the area of the ventral midbrain, where the SN is located. This decrease was by more than half compared to the controls. Striatal D1 as well as D2 receptor subtypes were also decreased due to this ID. Only a decrease in D2 receptors, was considered to be significant. DAT quantity was also decreased (43). This decrease would lead to less information being relayed via the pre synaptic cells, giving feedback on the extracellular dopamine concentrations. This in turn will cause an increase in production of dopamine and will also affect the daily variation in magnitude, of extracellular dopamine levels. What has been observed is that there is a great deal of circadian changes in dopamine levels in these RLS sufferers. The daily peak in dopamine levels may be higher and the daily low point decreased relative to controls. The current understanding is that he post synaptic dopamine receptors do not adapt appropriately to this daily fluctuations in dopamine concentration. What happens is that during the daily dip in dopamine concentration, does not lead to adequate dopamine production stimulation during this period. The circadian dip in dopamine levels is considered

to be the period of the day when patients with RLS will experience the characteristic symptoms of RLS. During the daily peak in dopamine concentration, this would correspond with the period of protection against RLS features (44). For example as one wakes up in the morning, during which they usually have a period of respite with no symptoms at all. Another interesting observation is that RLS patients usually decide to get out of bed and not continue sleeping, even though they may have suffered from the lack of sleep associated with RLS. This could possibly be due to morning dopamine levels being higher, helping them with the burden of the chronic effects of sleep deprivation, which would usually cause them to continue sleeping, with the inability to wake fully and easily. It is important to note that iron deficiency has helped us understand RLS to a greater degree as well as the effect dopamine has on the causation of RLS. It is also crucial to not forget about other neurotransmitters, such as adenosine for example. Studies have shown that dopamine is not the only neurotransmitters that could possibly be altered in these states, however more studies need to be undertaken to fully understand the complexity of theses influences on RLS disease course (45).

Iron deficiency is now regarded as one of the major causes of RLS, that has also now provided us with a better understanding of the pathology surrounding RLS. It is important to note that ID and RLS also interacts with other determinants that play a role in RLS. For example, people suffering from Rheumatoid Arthritis, seem to have a higher degree of RLS in comparison to the general population (46)(47). We know that RA studies have shown that iron status is also affected. The question that has arisen, is whether this RLS is actually secondarily linked to the iron status or whether this is solely linked to other factors in RA.

In summary, we have seen reduced brain levels of iron within the SN in RLS patients. By decreasing the amount of iron delivered to the brain, caused by a peripheral shortage leads to a higher likelihood of developing RLS. By administering iron supplementation therapy, RLS symptoms seem to improve drastically and for a subset of patient they even disappear completely. What is now also understood is that this link to ID and RLS also has an impact on the dopaminergic as well as other systems within the CNS. In vitro and in vivo studies have shown the effects of ID on the dopaminergic system. It is important that more studies are undertaken to evaluate and better understand the pathology of this disorder.

## Renal Disease

It has been shown that RLS has a higher prevalence in patients with chronic kidney disease (CKD) in comparison to the general population (48). Most of the studies have looked at end stage kidney disease sufferers receiving dialysis  CKD patients who are on dialysis have a prevalence between 12% to 25%, which is considerably higher than the general population, which is around 7.5% (49). Less studies have been undertaken in patients with earlier stages of CKD as well as patients who have received kidney transplantation. However the studies that have emerged, have demonstrated that patients who have had a kidney transplant have a prevalence of  RLS of 4.8% (50). It has also be demonstrated that kidney transplant recipients who develop RLS have a 2 times higher likelihood of dying (51). It has been shown time and time again that dialysis patients have a higher prevalence of RLS, however when looking at the International classification of diseases (ICD) codes used for diagnoses, only around 1% of dialysis patients have the co morbid diagnosis of RLS (52).This substantiates the fact that RLS is not well recognised in this population. The symptom presentation varies slightly in CKD in comparison to idiopathic (primary) RLS. The severity of RLS symptoms usually increase at a more rapid rate (53). It has also been noted that sleep disruptions are more prevalent in these CKD/RLS co sufferers.

With regards to the pathogenesis of RLS in CKD sufferers, it has been proposed that it is also linked to iron deficiency. Another interesting observation is that the more sudden the commencement of symptoms in dialysis patients, the higher probability the RLS is linked to a state of iron deficiency. In a study performed by Molnar et al., they found that patients receiving renal replacement therapy (RRT) had a convincingly reduced haemoglobin level and a higher degree of ID, with a significance of ($P < 0.05$) in comparison to the controls (54). A number of other possible causes have been studied. One possible risk is underdialysis as well as parathyroid dysfunction has been considered, in particular hypoparathyroidism. A genetic component has also now been discovered, which could influence the development of RLS in end stage kidney disease. Single nucleotide polymorphisms (SNPs) of the MEIS1 and BTBD9 type have been identified as a possible catalyst in the causation of RLS (55).

One of the ways to draw an association to kidney disease and RLS, is due the fact that the occurrence of RLS symptoms is altered by patients undergoing kidney transplantation. As the CKD progresses to a worsened state, marked by a decrease glomerular filtration rate and other measurable parameters, the rate of RLS increases. Once patients have undergone renal transplantation they show a drastic decrease in RLS. The prevalence of RLS decreases by almost 20% post transplantation(56). However more large scale studies need to be undertaken to continue to follow these patients with regards to the display and alterations of RLS symptoms post transplantation. One study also showed that patients receiving haemodialysis who were deficient in magnesium, also presented with an increase prevalence of RLS (57).

Disturbances in patients sleeping patterns are common among CKD sufferers. This has a large impact on the quality of life. A large proportion of RLS patients on dialysis have announced that that they suffer from extreme day time somnolence. Studies also showed that RLS sufferers with CKD, were more inclined to experience serious insomnia (19% higher in comparison to non-RLS CKD patients.)(58). Another important consideration is cardiovascular disease, which is much more prevalent in patients with CKD. Rates of hypertension seem to be higher in CKD RLS patients in comparison to CKD patients without RLS(59). Further studies also found that patients who were receiving RRT who have RLS, had a higher chance of developing new onset cardiovascular events in comparison to non RLS patients. CV events in the RLS/CKD dialysis group had a 64.5% chance. In comparison to non- RLS/CKD dialysis group of a 39.1% chance of adverse CV events ( $P<0.02$). (60). Another crucial finding in the research undertaken, is that patients with RLS receiving dialysis had a 32.2% chance of mortality, in comparison to the 14.5% chance of mortality in those patients who did not have RLS, but were also receiving dialysis for CKD (61)(62). These results of mortality rate are rather alarming. Importantly this study also comprised of patients with diabetes ( almost 1/3) as well as patients who underwent renal transplantation. The fact that these co morbid patients were included in this study, could lead to possible confounding elements. Therefore we cannot tell to what degree exactly these other co-morbidities contributed to the CV events and increased mortality. Patients suffering from combined RLS/CKD seem to have an overall decrease in QoL. Overall patients with both RLS and CKD have displayed signs of sleep problems, CV deterioration and reduced QoL. It is crucial to establish which of the CKD patients have RLS so that treatment can be commenced in order to improve the patients overall QoL(63)(64).

The issue with regards to treatment of patients with CKD and co-morbid RLS, is that patients are often required to sit for long periods of time during dialysis. Patients with a more severe RLS disease presentation, will often struggle to sit for long periods of time during dialysis. Some evidence points to physical exercise as a means to reduce RLS symptoms and have a good impact on the QoL. Unfortunately this has not shown to improve quality of sleep on patients receiving RRT (65). By moving RRT sessions to morning time slots, have helped with the symptomatic burden of RLS, which is usually better in the morning. The studies have shown that patients who receive dialysis in the afternoon or early evening had a 34.4% reported RLS symptom burden, in comparison to those who received dialysis in the morning, who reported a symptomatic burden of only 27.6%(66). Also the overall risk of developing RLS is increased in patients receiving haemodialysis in the afternoon compared to the morning. (odds ration 1.35; 95% confidence interval, 1.03-1.77, n=1450). A cohort study by the name of FREEDOM cohort, was conducted to show the effects of short daily haemodialysis (SDHD). It was shown that patients who received SDHD, displayed a reduction of RLS symptoms by 9%. Also patients who previously reported to have had moderate to severe symptoms experienced a decrease by 16%. One interesting finding is that sleep disruptions also were decreased after receiving 1 year of SDHD treatment (67). These findings look promising, however further comparisons need to be done. Other patients receiving normal dialysis in a comparable clinical environment, need to also be considered for a more accurate observation.

Another important consideration in RLS and CKD as a secondary cause of RLS, is that potential treatment issues must not be overlooked. This is due to the fact they may not be able to effectively excrete some drugs and there metabolites. Gabapentin for example has shown to decrease RLS symptoms in patients receiving dialysis. Two different studies were done and both were compared with levodopa and placebos, showing the marked effectiveness of gabapentin in these subset of patients (68). Gabapentin also proved to be more effective at relieving sleep disturbances in dialysis patients. Pregabalin for example has been used and proved to be effective for idiopathic RLS, however no studies have yet to be undertaken to see its effects on RLS patients receiving dialysis.

In summary, RLS has a higher prevalence in CKD than the general population. Even though it is more common it is often still missed and very much underdiagnosed. Due to the burden of symptoms, some patients may even discontinue dialysis treatment due to the discomfort and severity of symptoms they may experience during there dialysis. This is often due the long

periods of inactivity during dialysis. Studies have shown that patients on dialysis who also suffer from RLS are twice as likely to abandon dialysis before the end of the therapy session. Also 20% have reported that they had left their dialysis appointment early on at least one occasion or more (69). It is important to note that RLS brought on by CKD can be treated and managed, with both pharmacological and non-pharmacological modalities. It is important that further studies be undertaken to study the pathogenesis in more detail. Iron supplementation studies also need to be further studied so that a more accurate conclusion can be drawn. We know that CKD can lead to iron deficient states, as we see in many chronic diseases, represented by ACD, whether this is the exact cause, we still do not know. Regardless of the cause of RLS in CKD, we can still put emphasis on recognising RLS in these patients in order to start treatment early and provide some relief of symptoms. More studies must still be undertaken to seek improved treatments to improve QoL.

## Parkinson's Disease

It has widely been shown that RLS presents in disorders that involve the dopaminergic system. This finding as well as the response to dopaminergic treatment in RLS, has led to the preposition that dysfunction of the dopaminergic system occurs in patients with RLS. Autopsy studies performed on Parkinson's disease patients have shown the loss of neurons within the SN, leading to the loss in striatal dopamine. What has been found is that these lesions of neuron loss show a varying pattern of distribution. This pattern can be linked to the various subtypes of PD. For example, the ventrolateral part of the substantia nigra pars compacta (SNPC) that projects to the dorsal putamen, shows cell loss in this region. This is the more common pattern in the akinetic/rigid subtype of PD (70). In patients with a more tremor dominant type of PD, seem to display a more prevalent cell loss within the medial part of the SNPC. This degree of variation in patterns of cell loss, might illustrate why a subset of patients might develop RLS. In 8 of the patients with confirmed RLS, on post mortem examination showed a rather large decrease in dopamine receptors(D2) in the putamen region. This was regarded as significant in comparison to the control group. It was also found that this loss in D2 receptors was also directly proportional to the severity of the RLS symptoms (71).

These findings lead to a stringer body of evidence that PD and RLS could be associated. Within the SN, tyrosine hydroxylase was also increased in these patients. These findings of increased tyrosine hydroxylase were not increased in putamen of these RLS sufferers.It is important to mention that this discovery of increased phosphorylated tyrosine kinase, holds true to the evidence presented earlier in ID related to RLS, where increased presynaptic dopamine activity was also increased (44).

Several studies have been done to look at the link between PD and RLS clinically, after the criteria set out by the IRLSSG was introduced. The findings of these studies showed varied results. A Japanese population study found that RLS was significantly higher amongst PD patients in comparison to the controls, with an almost 10% higher prevalence. The study did show that the patients with PD and RLS were of a younger age compared to the PD patients without RLS. In Austria a cohort study was undertaken involving 113 PD sufferers. The findings showed that almost 1 out of 4 PD Patients with co morbid RLS were younger (63.1 vs 68.8, $P < 0.004$).These younger individuals also received lower dosages of levodopa (72).

Another study conducted in Brazil demonstrated a prevalence of 18.75% in their small sample group of 48 patients. It has been proposed that long standing treatment with anti-Parkinson drugs might be the contributing factor to the development of RLS instead of the actual pathology of PD (73). In Korea a study found that 16.3% of PD patients also had RLS. This study reported that the length of Parkinson treatment seemed to be the most profound factor leading to the onset of RLS in this study group (74).It is important to note that several studies also did not find significant co-morbid PD and RLS (75). Calzetti et al., in their case control study did not find an increase prevalence of RLS that would be considered significant (76). This was compared to gender and age related controls. In the Netherlands a study comprising 269 Caucasian individuals found a prevalence of co morbid RLS and PD to be around 11%, this is therefore considered to be in line with the general population prevalence. The only finding that was significant was that PD sufferers with RLS were more likely to be female ( $P< 0.001$) (77).

There was, however, a directly proportional relationship to the severity of PD and the severity of RLS. The study did, however, point out that the overall prevalence of RLS in this subject group could have possibly been under predicted because of the dopaminergic treatment the patients were receiving. A study in Singapore was conducted in a case control manor of 400 subjects. They found only a weak link between RLS and PD, with a RLS prevalence of 3% in the RLS-PD group and 0.5% in the control group ($P=0.07$) (78).

Brain imaging studies have been done in patients with PD and RLS. These functional imaging studies have shown a decrease in 18F-dopa uptake in PD patients (79). This study was also performed in RLS patients, but the results were unconvincing (80). A few studies demonstrated a small reduction in dopamine status on the post synaptic side. Sonographic studies in a sample size of 41 participants with RLS, 19 participants with RLS-PD and 25 others with only PD were studied. What was found is that on ultrasound there was a echogenic decrease in the region of the substantia nigra (SN) in the idiopathic RLS patients ($P< 0.0001$) (81). Another observation was in the PD-RLS patient group. The PD-RLS group actually showed an increase in echogenicity in the area of the SN in comparison to the controls ($P<0.05$). This points to the fact that there could be a different pathology in idiopathic PD, verses PD associated with RLS. Another study of PD patients found similar results(82).

Deep brain stimulation (DBS) is another topic of discussion with regards to co morbid PD-RLS. It has been reported that RLS has appeared in some patients post subthalamic nucleus DBS (83).11 people out of the almost 200 population study group demonstrated new onset of RLS symptoms after receiving DBS. It was noted that there was an almost ¾ decrease in the amount of Parkinson's disease medication usage post DBS. The researchers of this study proposed that this reduction in medication use due to the success of DBS, could well have potentially exposed the RLS symptoms, that were otherwise suppressed by the anti-parkinsonian drug treatments (84).

The general pathophysiological assumptions of the common pathway of RLS and PD, does encounter some issues. Firstly RLS in PD presents with more milder symptoms, than in patients with only PD. This could make it more difficult to recognise. Another issue is that once medication starts wearing off in PD patients, they could potentially present themselves with RLS like symptoms, an unfortunate complication of treatment with levodopa. Furthermore augmentation in RLS can occur from the long term use of dopaminergic drugs, such as levodopa in particular(85). In comparison PD sufferers start to experience dyskinesias and alterations in motor patterns from subsequent long term use of dopaminergic drugs such as levodopa. This is however not observed in RLS. Another crucial point to consider is that overall total iron levels and ferritin within the substantia nigra are elevated. This increase in iron leads to oxidative stress (86). This could potentially be the reason for the dopaminergic degeneration. On the complete contrary RLS is a disorder of ID, this has been demonstrated by low CSF ferritin values and high CSF transferrin values(87). Additionally various MRI imaging was used to detect brain iron values, as mentioned earlier in this review. It was shown that iron within the SN was decreased rather significantly in RLS in relation to controls, however iron concentrations were not as reduced in the putamen area of the basal ganglia (88). A transcranial ultrasound study on RLS patients found regions of reduced hyper-echogenicity in the midbrain when compared to the controls, when this hyper echogenicity in RLS patients was further compared to PD patients, the regions had even more reduced hyper-echogenicity in comparison to the controls(89).

Overall the connection between RLS and PD is still not fully understood. Many of the studies undertaken so far show some promising results and others show opposing results. Some of these findings have found an incidence of RLS in PD to be higher than in the general population. Others have simply found no increase in prevalence of RLS in PD patients in comparison to the

general population. It is important to continue to undertake long term observations of patients with PD and to watch for possible RLS onset and to monitor these changes. More studies need to be done over long periods of time in order to address the disparity between these findings in previous clinical research. It is also crucial that functional MRI studies are done on RLS-PD comparing them to PD only patients, this will give further insight into the underlying pathology of RLS in PD. Some studies have pointed out the decrease in D2 receptors in these patients, but more associations need to be looked into, possibly comparing the decrease D2 receptor quantity in RLS-PD patients verses in isolated RLS patients and isolated PD patients separately. The effect of dopaminergic medication and there long term use as well post DBS changes in levodopa treatment, leading to possible RLS onset and worsening of symptoms must not be overlooked either.

In conclusion some overlap does exist between these two entities. Dopaminergic abnormalities are present in both of these disorders. The certain components within the underlying pathology might be very different, with some of these observations already been proven by transcranial ultrasound. From a genetic point of view, only the parkin mutation has been linked to RLS, but no other genetic studies have shown a correlation to RLS and PD. There is still a lot to be explored with regards to the pathology RLS-PD.

## Pregnancy

The prevalence of RLS seems to be around 2 to 3 times higher in pregnant woman in comparison to non-pregnant woman (90).The studies have shown that the prevalence seems to be at its high point during the last trimester. Most studies reported similar findings. Interestingly a few studies found that there was no major increase in prevalence from the 2nd to the 3rd trimester, only from the 1st trimester to the 2nd or 3rd (91). Another important observation was detected in a study undertaken in Germany. They noticed that with the increasing number of times a woman has previously given birth (parity) the higher the likelihood of developing RLS in comparison to woman who have never given birth before (nulliparous) (92).

The pathophysiology of new onset RLS in pregnant woman can now be categorised into the various possible mechanisms that could be the reason for development of RLS in this subgroup. Hormonal influences could potentially have a major role in the development of RLS in these patients. During pregnancy oestrogen, progesterone, prolactin and thyroid hormones are raised, with values reaching a peak towards full term. Oestradiol levels are at their maximum values in the 3rd trimester. These levels decrease once the baby is delivered and so does the symptoms of RLS decreasing in a likewise manner. A significant finding was that 3rd trimester woman with RLS had a relatively higher level of oestradiol than in 3rd trimester pregnant woman without RLS, which points towards the possible role of this hormone in the development of RLS (93).The oestrogen hypothesis however has its sceptics. One study done by TunC et al., found that there was no significant variation between these oestradiol levels in pregnant woman with RLS verses pregnant woman without RLS (94). The study however failed to mention the number of participants in each group. This will potentially affect the overall significance of the study. Even though oestrogen is considered to be implicated we still don't know exactly how this could lead to RLS. Some animal models in rats gave some insight into the potential effects of oestrogen. Long term high levels of 17beta oestradiol lead to decreased levels of striatal dopamine receptiveness(95). It is important to point out that one of the roles of oestradiol is to decrease dopamine release from the from the anterior pituitary into the blood stream. This leads to a decrease in suppressive effects on lactotrophs. This is turn would increase prolactin levels, however so far there is no evidence of the association of prolactin as a contributing factor in the pathology of RLS. Progesterone is also elevated in the pregnant state and reaches a peak in the 3rd trimester. Yet we still do not know if this have any correlation to RLS development. Evidence does, however, point to the fact that progesterone and dopamine within the striatum

do interact in some way or another. Thyroid hormone has also been questioned as a potential implicate in RLS development. Findings have shown that there is an inverse relationship between TH and dopamine(96). HCG hormone stimulates TH in the first 2 to 3 months of pregnancy, so this would give inference into the potential decrease in dopamine in the 1st trimester but not give answers as to why this increase in RLS is highest in the 3rd trimester. Another angle that has been considered is that if the increased levels of progesterone and oestradiol are maintained for this long period of time during pregnancy, this will lead to a decrease in dopamine activity. This in turn would lead to an increase in TH which would lead to the state of RLS in pregnancy. However this hypothesis does not seem likely.

Yet again iron could be implicated in RLS in this subgroup of sufferers. Iron plays an important role as a co factor in the production of dopamine by the enzyme tyrosine hydroxylase. Folate is also crucial as it helps with the tetrahydrobiopterin production, which is also needed as a co factor for tyrosine hydroxylase (97). Therefore if we have a deficiency in either of these, dopamine synthesis will be compromised. In the pregnant state, iron and folate are usually decreased in comparison to the non-pregnant state, due to the many reasons that have to do with the physiology of pregnancy. Another study found that if blood ferritin levels were low before pregnancy, this indicated a higher possibility of RLS occurring during pregnancy (94). The most crucial outlier is that once pregnancy is complete the symptoms of RLS stop abruptly. During these early days when these symptoms cease, the iron and folate levels are usually still depleted and only recover over time. Therefore this mechanism cannot be considered as the leading factor in the pathophysiological development of RLS in pregnant woman.

Other possibilities to consider are the various psychological states that can surround pregnancy. Fatigue, anxiety, stress and insomnia are all possible factors that lead to the worsening of RLS symptoms(98). Another interesting possibility is the enlarging foetus causes a form of mechanical pressure on the Lumbosacral nerves, leading to the onset of RLS symptoms. This would disappear once the pressure is relieved by the delivery of the child(91).

Another study looked into the peripheral venous distention that occurs while pregnant (99). This will lead to pressure increases within the extremities due to the oedema, and this in turn would lead to a heightened stimulation of the somatosensory receptors possibly triggering RLS symptoms. These are however all hypotheses that lack a lot of substantial evidence. More studies would need to be done in order to prove these hypotheses.

Overall RLS in pregnancy has multiple potential causes that are often very complex to pinpoint. Hormones associated with pregnancy could very well play an important part in the development of RLS in pregnancy. Iron deficiency is another overlapping concern that needs to be treated. Many studies have looked at various treatment options for pregnant woman with RLS, in particular looking at whether these drugs are safe for mother and baby or whether the risks outweigh the benefits. It has been shown that some dopaminergic drugs as well as some benzodiazepines and antiepileptics can be used to treat these patients. What is important to point out is that most of these patients experience a full recovery from RLS once the pregnancy is over.

## Diabetes and Neuropathy

Many different types of neuropathies have been identified to have an increase prevalence of RLS. Some of these include disorders like diabetic neuropathy, poliomyelitis, motor neuron disease , alcohol associated as well as many other various types of neuropathies. Neuropathy on its own already has a high prevalence in the general population. The fact that both of these disorders are common , there is a chance that a high combination of both could possibly occur simultaneously incidentally. Many studies have looked at the co-existence of RLS and neuropathy. One study with almost 1000 patients who were suffering from diabetes, who also displayed some neuropathic elements only showed a 8.8% prevalence of RLS features. This was only around 1.8% higher than the controls, therefore not considered significant (100).There was one significant finding that found type 2 diabetics were significantly more affected with RLS, than type 1 diabetics ($P<0.02$). this however could be due to the fact that type 2 diabetics were of an older age. Another study looked at a group of patients who were diagnosed with neuropathy and in all 154 patients, they followed the IRLSSG criteria for diagnosing RLS. They reported a prevalence of 5 %. This is considered to be in line with the standard prevalence in the general population and might even be considered to be lower (101).

It is important to note that various forms of neuropathies all show different prevalence patterns of RLS. Charcot Marie Tooth II which is considered to be of an axonal neuropathy, showed a 37% occurrence of RLS (10/27). Interestingly the study also looked at the other 17 patients with Charcot Marie Tooth I which is a demyelinating neuropathy. In these patients not one was found to have had RLS (102). In another series of studies just over one third of RLS sufferers showed signs of neuropathy, detected by electrophysiological studies and conduction velocity studies. The majority of these patients suffering from neuropathies, were of the axonal subtype. The aetiology of the neuropathy varied from patient to patient. The overall prevalence of neuropathy was considerably higher in those patients who had no previous family association to RLS, in comparison to the ones who did have a family history of RLS ($P<0.001$), leading to a possible stronger evidence base of this being of a secondary nature (103). Another study also found that patients suffering from small fibre neuropathies had an increase prevalence of RLS (104). Small fibre neuropathies could also possibly go undetected when presenting with RLS as they can only be detected by biopsy examination.

Patients presenting with a neuropathic associated RLS, might have a different presentation of RLS symptoms. Such as these patients might have specific neuropathic pain. This pain is usually of the burning character and less deep. This contrast between the pain type and the urge to move is often not differentiable by the suffer. Lastly an interesting finding is that augmentation with the long term use of dopaminergic drugs is not common in patients with neuropathy associated RLS compared to other RLS sufferers.

Many studies have looked at the association of diabetes mellitus and RLS. Some studies have found the overall prevalence to be around 4 times greater than the non-diabetic general population, with other studies not showing as high rates. Because there has been a strong connection between underlying neuropathies as a trigger for RLS, this could potentially be the reason for the higher prevalence of RLS in diabetic patients. Since diabetic neuropathy is one of the main components of diabetes.

## Myelinopathy

Multiple articles have demonstrated that the spinal cord plays an important role in the pathology of RLS. This has been shown by evidence of reduced inhibition in the spinal cord. Another observation in some is that anaesthesia given regionally into the spine has exacerbated RLS symptoms. This was demonstrated by a study that followed patients post spinal anaesthesia. 8.7% of patients who had no previous history of RLS, developed RLS symptoms shortly after the procedure (105). Also any lesion that affect the spinal cord, such as traumatic events, infectious or even neoplastic infiltrations, all lead to an increase in RLS and PLMS. These symptoms did disappear after roughly one month. These patients have responded well to treatment for RLS and physiotherapy. However a lot more studies with regards to treatment, still need to be undertaken.

## Fibromyalgia

In a cross sectional study design undertaken in the United Sates, they found an increased prevalence of RLS in Fibromyalgia. They found a prevalence of 33% in the Fibromyalgia group in comparison to the 3.1 % in the controls who did not suffer from fibromyalgia (106). This was all adjusted in order to reflect appropriate age and gender. It was also detected that sleep was also more disturbed in the RLS-FM group in comparison to the controls. Overall there is an increased risk of developing RLS in patients with fibromyalgia than in the general population without fibromyalgia. It is crucial to note that both these disorders are not fully understood yet. However both draw links to the CNS and various neuronal processing and feedback. The problem in this co existing RLS-FM disorder is that RLS significantly affects sleep. Fibromyalgia on the other hand relies on sleep as a means of treatment and as a way to relieve symptoms (106). Therefore RLS often exacerbates Fibromyalgia. Even though the cause may be unknown, it is important that we treat the sleep issues brought on by the RLS, in this patient group. This will improve the patients quality of life and reduce the symptoms of both RLS and Fibromyalgia. It is also important that fibromyalgia patients suffering from sleep disturbances and possible RLS symptoms, be screened using the IRLSSG criteria for RLS as well.

## Multiple Sclerosis

Many various studies reviewed the possible co-existence of RLS and Multiple sclerosis. The majority found a higher occurrence of RLS in MS in comparison to those without MS. The interestingly finding is that in over 10 different studies the prevalence varied from as low as 13% to some finding an almost 2/3 occurrence of RLS in MS (107). The primary progressive variant of MS was the more common variant seem in RLS co-sufferers. This may give some insight in to the possible difficulties of defining RLS in MS patients, and therefore could pose a challenge in determining the true significance of their findings. Some features of MS might just mimic RLS. The possible theoretical link still is not well defined yet and more studies need to be done. However the current thought, is that the spinal lesions seen in MS could lead to increased PLMS. Also that these lesions can also potentially lead to sensory disruptions which could present as RLS(108). It is therefore imperative that RLS found in MS be accurately diagnosed and treated, with new studies focusing on how the co-existence of RLS occurs and what impact it may have on QoL of these patients with MS.

## Ataxias

A study by Abele et al. found that RLS occurred in almost one third of the patients they studied with various ataxias (109). These patients all had genetic associated ataxias, such as spinocerebellar ataxia 1,2 and 3. In their findings they found an average onset of RLS to be at 49 years of age. They also found no association between the length of nucleotide repeats and RLS. They did however notice that the longer the neurological symptoms of SCA occurred ,the higher likelihood of development of RLS over time. Another study observed a prevalence of close to half of their subjects to have RLS- ataxia. They however said this was only observes in SCA type 3. The occurrence of RLS in type 1 SCA and type 2 SCA uncommon according to their findings. They also reported on the fact that patients with SCA-3 and co existing RLS had family members without SCA-3 who had no signs or symptoms of RLS (110). This would lead to the possible secondary and non-genetic link of SCA-RLS. Unfortunately there is not much data on treatment strategies in these subset of patients and whether they respond well or not to the conventional treatment regimens for RLS.

## Essential tremor

In a study of one hundred participants who had an essential tremor (ET), one third of the participants were diagnosed with RLS according to the IRLSSG criteria (111). In this group of 33 patients more than half stated that they had a family history of RLS. Importantly the only significant prognostic element for the increased risk of the development of RLS in ET patients, was a positive family history. In conclusion there was a rather high rate of ET patients who previously went undiagnosed with co morbid RLS. However when looking at other causes of secondary RLS, where family history usually did not play an important part in the relative risk of the development of RLS, in contrast tremor patients, family history was an important factor. This points to the fact that a genetic element could potentially be responsible for this link. Another important finding was that a few families were discovered to have had ET plus RLS. A certain gene locus was identified in these families. It was identified on the 2p chromosome ET gene area. This was discovered in around 30 family members who reported symptoms of RLS as with there ET. The study also showed that DBS for the tremor did not lead to improvement of their RLS features.

## Stroke

Five different studies displayed interesting findings with regards to the link between stroke and RLS. Firstly no real increased risk was detected for a stroke in RLS patients (112). However patients who suffered a stroke already, could possibly have an increased risk for the secondary development of RLS in comparison to the general population without a previous stroke. This general increase prevalence of RLS, could be due to the relative cardiovascular risk associated with a stroke. Another potential hypotheses is that the specific location of the stroke, could potential occur in a location that triggers the onset of RLS- ”sensitive RLS area” (108). This has been observed in regions where a stroke occurred in the basal ganglia and pons that lead to a higher occurrence of post stroke induced RLS. Therefore these regions could be considered as possible trigger zones for RLS.

## Cardiovascular disease

Cardiovascular disease (CVD) has been widely studied in all spheres of medicine. The link to RLS has also now been widely studied in recent years. CVD in RLS studies, comprises of coronary artery disease as well as valvular diseases. Two different studies both showed and increased prevalence of RLS in patients who had a reduced coronary blood flow. The increased prevalence was around 10 to 20% higher in comparison to those who were considered to have had a normal coronary flow (113)(114). It is thought that endothelial dysfunction is the possible culprit in this higher risk of RLS. Many other large scale studies could not find an increase prevalence of RLS in CVD patients. In general there is still only weak evidence that CVD leads to higher rates of RLS. It is important to also question the fact that CVD as an entity on its own, is a large burden and often presents with many other co morbidities. These ”other” co morbidities could potentially be the reason for the possible increase in these patients. However a lot more research would still need to be done in this field to draw a conclusion to this increased risk.

## Miscellaneous

Many other disorders have been widely studied with regards to the possible connection to RLS. One of the findings pointed towards the association of RLS to Tourette syndrome (TS) (115). The tics which are present in TS, in particular the leg tics can resemble RLS. It is interestingly to note that both these disorders are linked to dopaminergic dysfunction. Still there is no accurate evidence pointing to an increase in RLS prevalence in TS patients. Sleep apnoea has also now been linked to higher rates of PLMS in comparison to the general population. However there is little data confirming this association. A study from 2005 find that 8% of their sleep apnoea study subjects had RLS, in comparison to their controls who had only a 2.5% prevalence of RLS (116). Another study found an increase prevalence in RLS, in patients who suffered from familial spastic paresis (117). This is just a few of the many possible associations found in various literature sources. It is important to point that many of these numerous connections to RLS do not have sufficient evidence to support their findings. Due to the high prevalence of RLS in the general population, it is difficult to separate some of these associations with the possibility of RLS occurring due to pure chance in these subjects.

## Treatment for RLS

As we already know RLS is a common disorder amongst the general population. It is essential to mention the fact that not all people need treatment. For some people non pharmacological treatment my be sufficient. Roughly 85% of RLS sufferers have a mild disease course. The other 15% with moderate and severe disease will gain improvement with the help of specialised treatment strategies. It is important that patients with the mild form of RLS be informed that RLS is by no means life threatening. It is also crucial to mention to the patient that RLS is also not a psychological disorder. Some self-help measures could assist these patients to relive their symptoms to some degree.

Self-help activities would include; Warm and cold baths, walking, distraction while sitting, massaging, swimming and good sleep hygiene. Good sleep practices such as avoiding alcohol before going to sleep as well as tea and coffee. Going to bed at a similar time each night helps with a good circadian pattern, which seems to benefit RLS patients to some degree.

It is also important to be aware that some medications may exacerbate RLS. Some of these include drugs like; some tricyclic anti-depressants, anti-emetics, phenytoin as well as large quantities of caffeine can all worsen RLS features.

For patients with more severe symptoms, they might require pharmacologic treatment. Before any of these patients are started of pharmacological agents it is important to check ferritin levels. Patients found to have low ferritin, should first start on oral iron treatment. This might improve the RLS.

**Dopamine agonists**. These are the first line drugs used in RLS. These usually alleviate symptoms in 70 to 100 percent of patients. These drugs include examples such as ropinirole and pramipexole. In comparison there dosages for RLS are lower than in Parkinson's disease patients.

**Levodopa**. This was previously a first line choice, however this is no longer the case. Levodopa has a high degree of augmentation and rebound phenomenon., hence why its use isn't as common as before.

**Anti-epileptics**. These can be used in patients who do not respond to dopamine agonist therapy. Gabapentin is often the drug of choice.

**Benzodiazepines**. In a few patients who do respond to other lines of pharmacological treatment such as dopamine agonists, may still struggle with sleep onset or remaining asleep. In these patient drugs such as clonazepam can be used for the insomnia/sleep disturbance.

**Opiates.** Patients who suffer from severe RLS that does not remit may require treatment with opiates. The opiates used are usually drugs such as codeine, oxycodone and tramadol. It is however important that these patients be closely monitored.

**Apomorphine**. For rare cases of total pharmacological unresponsiveness, patients may need to be admitted to hospital. In some of these cases they will need administration of a very strong dopamine agonist such as apomorphine, give as a subcutaneous infusion.

Most cases of RLS can be managed by a non-specialist in the primary healthcare setting. If the diagnosis is questionable and the patient is not responsive to the treatment regimen then referral to a neurologist is warranted.

## The Future of RLS

The future for RLS looks bright. The contemporary findings of new gene variants, allows for more in depth studies of these genes and how they might increase the risk of RLS development. These studies may also give more insight into the underlying pathophysiology of this disorder. The more studies around possible secondary causes will also give further insight into the epidemiological situation that surrounds RLS. All these studies will also give a more accurate account of the negative aspects of RLS, such as the associated features of sleep disturbances and fatigue. More drug trials are underway with modes of delivery, other than the conventional oral route, which may further help relieve symptoms of RLS.

## Conclusion

RLS now has a few well defined secondary causes. The secondary causes of RLS would include iron deficiency, renal disease as well as pregnancy. There is still strong evidence thatsuggests a link between RLS and Parkinson's disease, Essential Tremor, various ataxias and some Neuropathies, however more widespread long term studies need to be undertaken to cement these associations. There are multiple other studies that have described other associations, however they still lack sufficient evidence. Nonetheless, it is important that RLS sufferers are identified and that a neurological exam is performed to look for any other neurological abnormalities. It is important that secondary causes are looked for, such as getting an iron profile for ID, electrolyte status as well as screening for kidney disease. If a neuropathy is found then ordering electromyographic studies as well as getting thyroid function tests and B12/folate levels, would be considered appropriate. Treatment for secondary RLS is essentially the same as for primary RLS. However more specific studies for specialised treatments orientated towards the specific secondary cause, still need to be further researched.

## Acknowledgments

I would like to thank my mentor, Professor Srđana Telarović, for her academic guidance throughout this process. I would like to thank the University of Zagreb, School of Medicine for giving me the opportunity to follow my dream. I would also like to thank my parents and fiancé for their unwavering support throughout my entire medical degree and this review paper. To my Croatian "parents," Tanja and Ivo, for their familial support role to me during my time in Zagreb. And lastly, to my dear Pahuljica for keeping me company over the past six years and getting me out for fresh air during our regular walks in Ribnjak park.

## References


1. Byrne R, Sinha S, Chaudhuri KR. Restless legs syndrome: diagnosis and review of management options. Neuropsychiatr Dis Treat. 2006 Jan;2(2):155–64.

2. Ekbom K, Ulfberg J. Restless legs syndrome. J Intern Med. 2009 Nov;266(5):419–31.

3. Coccagna G. Restless legs syndrome: an historical note. Sleep Med. 2004 May;5(3):279–83.

4. Konofal E, Karroum E, Montplaisir J, Derenne J-P, Arnulf I. Two early descriptions of restless legs syndrome and periodic leg movements by Boissier de Sauvages (1763) and Gilles de la Tourette (1898). Sleep Med. 2009 May;10(5):586–91.

5. Cortese S, Lecendreux M, Bernardina BD, Mouren MC, Sbarbati A, Konofal E. Attention-deficit/hyperactivity disorder, Tourette's syndrome, and restless legs syndrome: The iron hypothesis. Med Hypotheses. 2008 Jan;70(6):1128–32.

6. Figorilli M, Puligheddu M, Congiu P, Ferri R. The Clinical Importance of Periodic Leg Movements in Sleep. Curr Treat Options Neurol. 2017 Mar;19(3):10.

7. Walters AS, Aldrich MS, Allen R, Ancoli-Israel S, Buchholz D, Chokroverty S, et al. Toward a better definition of the restless legs syndrome: BETTER DEFINITION OF RLS. Mov Disord. 1995 Sep;10(5):634–42.

8. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med. 2003 Mar;4(2):121–32.

9. Manconi M, Ulfberg J, Berger K, Ghorayeb I, Wesström J, Fulda S, et al. When gender matters: Restless legs syndrome. Report of the "RLS and woman" workshop endorsed by the European RLS Study Group. Sleep Med Rev. 2012 Aug;16(4):297–307.

10. Maheswaran M, Kushida CA. Restless legs syndrome in children. MedGenMed Medscape Gen Med. 2006 Jun 20;8(2):79.

11. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless Legs Syndrome Prevalence and Impact: REST General Population Study. Arch Intern Med. 2005 Jun 13;165(11):1286.

12. Gupta R, Dhyani M, Kendzerska T, Pandi-Perumal SR, BaHammam AS, Srivanitchapoom P, et al. Restless legs syndrome and pregnancy: prevalence, possible pathophysiological mechanisms and treatment. Acta Neurol Scand. 2016 May;133(5):320–9.

13. Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet. 2007 Aug;39(8):1000–6.

14. Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, et al. A Genetic Risk Factor for Periodic Limb Movements in Sleep. N Engl J Med. 2007 Aug 16;357(7):639–47.

15. Dhawan V, Ali M, Chaudhuri KR. Genetic aspects of restless legs syndrome. Postgrad Med J. 2006 Oct;82(972):626–9.

16. Wijemanne S, Ondo W. Restless Legs Syndrome: clinical features, diagnosis and a practical approach to management. Pract Neurol. 2017 Dec;17(6):444–52.

17. Milligan SA, Chesson AL. Restless Legs Syndrome in the Older Adult: Diagnosis and Management. Drugs Aging. 2002;19(10):741–51.

18. Trenkwalder C, Paulus W. Why do restless legs occur at rest?—pathophysiology of neuronal structures in RLS. Neurophysiology of RLS (part 2). Clin Neurophysiol. 2004 Sep;115(9):1975–88.

19. Walters AS. Chapter 22 Restless legs syndrome and periodic limb movements in sleep. In: Handbook of Clinical Neurophysiology [Internet]. Elsevier; 2005 [cited 2021 Apr 8]. p. 273–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1567423109700474

20. Ferri R, Manconi M, Plazzi G, Bruni O, Cosentino FII, Ferini-Strambi L, et al. Leg movements during wakefulness in restless legs syndrome: Time structure and relationships with periodic leg movements during sleep. Sleep Med. 2012 May;13(5):529–35.

21. Karroum EG. Painful Willis-Ekbom disease: *unbearable and distinct form of restless legs?* Scand J Pain. 2019 Jul 26;19(3):429–31.

22. By K. Ray Chaudhuri, C. Warren Olanow, Per Odin. Restless legs syndrome.

23. Ruppert E. Restless arms syndrome: prevalence, impact, and management strategies. Neuropsychiatr Dis Treat. 2019;15:1737–50.

24. Bogan RK. Effects of restless legs syndrome (RLS) on sleep. Neuropsychiatr Dis Treat. 2006 Dec;2(4):513–9.

25. Kurlan R, Richard IH, Deeley C. Medication tolerance and augmentation in restless legs syndrome: the need for drug class rotation. J Gen Intern Med. 2006 Dec;21(12):C1-4.

26. Kalloo A, BA Candidate, Department of Neuroscience, Johns Hopkins University, Gamaldo CE, Associate Professor, Department of Neurology, Sleep Division, Johns Hopkins University School of Medicine, Kwan AB, BA, Department of Neuroscience, Johns Hopkins University, et al. The Impact of Restless Legs Syndrome/ Willis–Ekbom Disorder on Quality of Life. Eur Neurol Rev. 2013;8(2):97.

27. Koo BB, Bagai K, Walters AS. Restless Legs Syndrome: Current Concepts about Disease Pathophysiology. Tremor Hyperkinetic Mov N Y N. 2016;6:401.

28. Wali SO, Abaalkhail B. Prevalence of restless legs syndrome and associated risk factors among middle-aged Saudi population. Ann Thorac Med. 2015 Sep;10(3):193–8.

29. Allen RP, Earley CJ. The role of iron in restless legs syndrome. Mov Disord. 2007;22(S18):S440–8.

30. Guyatt GH, Patterson C, Ali M, Singer J, Levine M, Turpie I, et al. Diagnosis of iron-deficiency anemia in the elderly. Am J Med. 1990 Mar;88(3):205–9.

31. Means RT, Allen J, Sears DA, Schuster SJ. Serum soluble transferrin receptor and the prediction of marrow aspirate iron results in a heterogeneous group of patients. Clin Lab Haematol. 1999 Jun;21(3):161–7.

32. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. Sleep Med. 2009 Oct;10(9):973–5.

33. Bartzokis G, Beckson M, Hance DB, Marx P, Foster JA, Marder SR. MR evaluation of age-related increase of brain iron in young adult and older normal males. Magn Reson Imaging. 1997 Jan;15(1):29–35.

34. Earley CJ, B Barker P, Horská A, Allen RP. MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Med. 2006 Aug;7(5):458–61.

35. Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology. 2001 Jan 23;56(2):263–5.

36. Schmidauer C, Sojer M, Seppi K, Stockner H, Högl B, Biedermann B, et al. Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. Ann Neurol. 2005 Oct;58(4):630–4.

37. Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. J Sleep Res. 2005 Mar;14(1):43–7.

38. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology. 2000 Apr 25;54(8):1698–700.

39. Earley CJ, Connor JR, Beard JL, Clardy SL, Allen RP. Ferritin levels in the cerebrospinal fluid and restless legs syndrome: effects of different clinical phenotypes. Sleep. 2005 Sep;28(9):1069–75.

40. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology. 2003 Aug 12;61(3):304–9.

41. Connor JR, Wang XS, Patton SM, Menzies SL, Troncoso JC, Earley CJ, et al. Decreased transferrin receptor expression by neuromelanin cells in restless legs syndrome. Neurology. 2004 May 11;62(9):1563–7.

42. Chen Q, Connor JR, Beard JL. Brain iron, transferrin and ferritin concentrations are altered in developing iron-deficient rats. J Nutr. 1995 Jun;125(6):1529–35.

43. Erikson KM, Jones BC, Beard JL. Iron deficiency alters dopamine transporter functioning in rat striatum. J Nutr. 2000 Nov;130(11):2831–7.

44. Connor JR, Wang X-S, Allen RP, Beard JL, Wiesinger JA, Felt BT, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain J Neurol. 2009 Sep;132(Pt 9):2403–12.

45. Quiroz C, Gulyani S, Ruiqian W, Bonaventura J, Cutler R, Pearson V, et al. Adenosine receptors as markers of brain iron deficiency: Implications for Restless Legs Syndrome. Neuropharmacology. 2016 Dec;111:160–8.

46. Salih AM, Gray RES, Mills KR, Webley M. A CLINICAL, SEROLOGICAL AND NEUROPHYSIOLOGICAL STUDY OF RESTLESS LEGS SYNDROME IN RHEUMATOID ARTHRITIS. Rheumatology. 1994;33(1):60–3.

47. Taylor-Gjevre RM, Gjevre JA, Skomro R, Nair B. Restless legs syndrome in a rheumatoid arthritis patient cohort. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2009 Feb;15(1):12–5.

48. Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, et al. Restless legs syndrome in end-stage renal disease. Sleep Med. 2004 May;5(3):309–15.

49. Lin C-H, Wu V-C, Li W-Y, Sy H-N, Wu S-L, Chang C-C, et al. Restless legs syndrome in end-stage renal disease: a multicenter study in Taiwan. Eur J Neurol. 2013 Jul;20(7):1025–31.

50. Molnar MZ, Novak M, Ambrus C, Szeifert L, Kovacs A, Pap J, et al. Restless Legs Syndrome in patients after renal transplantation. Am J Kidney Dis Off J Natl Kidney Found. 2005 Feb;45(2):388–96.

51. Cubo E, Gallego-Nieto C, Elizari-Roncal M, Barroso-Pérez T, Collazo C, Calvo S, et al. Is Restless Legs Syndrome Associated with an Increased Risk of Mortality? A Meta-Analysis of Cohort Studies. Tremor Hyperkinetic Mov N Y N. 2019;9.

52. Kutner NG, Zhang R, Bliwise DL. Restless legs syndrome is underdiagnosed in the US Renal Data System. QJM Mon J Assoc Physicians. 2013 May;106(5):487.

53. Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep. 2000 Aug 1;23(5):597–602.

54. Molnar MZ, Novak M, Mucsi I. Management of restless legs syndrome in patients on dialysis. Drugs. 2006;66(5):607–24.

55. Schormair B, Plag J, Kaffe M, Gross N, Czamara D, Samtleben W, et al. MEIS1 and BTBD9: genetic association with restless leg syndrome in end stage renal disease. J Med Genet. 2011 Jul;48(7):462–6.

56. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. Mov Disord Off J Mov Disord Soc. 2002 Sep;17(5):1072–6.

57. Collado-Seidel V, Kohnen R, Samtleben W, Hillebrand G, Oertel W, Trenkwalder C. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. Am J Kidney Dis. 1998 Feb;31(2):324–8.

58. Molnar MZ, Novak M, Szeifert L, Ambrus C, Keszei A, Koczy A, et al. Restless legs syndrome, insomnia, and quality of life after renal transplantation. J Psychosom Res. 2007 Dec;63(6):591–7.

59. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007 Jul 3;116(1):85–97.

60. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology. 2008 Jan 1;70(1):35–42.

61. Li Y, Wang W, Winkelman JW, Malhotra A, Ma J, Gao X. Prospective study of restless legs syndrome and mortality among men. Neurology. 2013 Jul 2;81(1):52–9.

62. La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML, et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2011 Jun;26(6):1976–83.

63. Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB, et al. Restless legs symptoms among incident dialysis patients: association with lower quality of life and shorter survival. Am J Kidney Dis Off J Natl Kidney Found. 2004 May;43(5):900–9.

64. Kutlu R, Selcuk NY, Sayin S, Kal O. Restless legs syndrome and quality of life in chronic hemodialysis patients. Niger J Clin Pract. 2018 May;21(5):573–7.

65. Iliescu EA, Yeates KE, Holland DC. Quality of sleep in patients with chronic kidney disease. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2004 Jan;19(1):95–9.

66. Lin X-W, Zhang J-F, Qiu M-Y, Ni L-Y, Yu H-L, Kuo S-H, et al. Restless legs syndrome in end stage renal disease patients undergoing hemodialysis. BMC Neurol. 2019 Dec;19(1):47.

67. Jaber BL, Schiller B, Burkart JM, Daoui R, Kraus MA, Lee Y, et al. Impact of short daily hemodialysis on restless legs symptoms and sleep disturbances. Clin J Am Soc Nephrol CJASN. 2011 May;6(5):1049–56.

68. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of Restless Legs Syndrome in hemodialysis patients: an open-label study. Ren Fail. 2004 Jul;26(4):393–7.

69. Scherer JS, Combs SA, Brennan F. Sleep Disorders, Restless Legs Syndrome, and Uremic Pruritus: Diagnosis and Treatment of Common Symptoms in Dialysis Patients. Am J Kidney Dis Off J Natl Kidney Found. 2017 Jan;69(1):117–28.

70. Jellinger KA. Recent developments in the pathology of Parkinson's disease. J Neural Transm Suppl. 2002;(62):347–76.

71. Peeraully T, Tan E-K. Linking restless legs syndrome with Parkinson's disease: clinical, imaging and genetic evidence. Transl Neurodegener. 2012 Feb 27;1(1):6.

72. Peralta CM, Frauscher B, Seppi K, Wolf E, Wenning GK, Högl B, et al. Restless legs syndrome in Parkinson's disease. Mov Disord Off J Mov Disord Soc. 2009 Oct 30;24(14):2076–80.

73. Guerreiro TM, Nishikawa DRC, Ferreira LC, Melo HA de, Prado RCP do. Restless legs syndrome in Parkinson's disease: clinical characteristics and biochemical correlations. Arq Neuropsiquiatr. 2010 Dec;68(6):869–72.

74. Lee JE, Shin H-W, Kim KS, Sohn YH. Factors contributing to the development of restless legs syndrome in patients with Parkinson disease. Mov Disord Off J Mov Disord Soc. 2009 Mar 15;24(4):579–82.

75. Calzetti S, Negrotti A, Bonavina G, Angelini M, Marchesi E. Absence of co-morbidity of Parkinson disease and restless legs syndrome: a case-control study in patients attending a movement disorders clinic. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2009 Apr;30(2):119–22.

76. Calzetti S, Angelini M, Negrotti A, Marchesi E, Goldoni M. A long-term prospective follow-up study of incident RLS in the course of chronic DAergic therapy in newly diagnosed untreated patients with Parkinson's disease. J Neural Transm Vienna Austria 1996. 2014 May;121(5):499–506.

77. Verbaan D, van Rooden SM, van Hilten JJ, Rijsman RM. Prevalence and clinical profile of restless legs syndrome in Parkinson's disease. Mov Disord Off J Mov Disord Soc. 2010 Oct 15;25(13):2142–7.

78. Tan EK, Lum SY, Wong MC. Restless legs syndrome in Parkinson's disease. J Neurol Sci. 2002 Apr 15;196(1–2):33–6.

79. Michaud M, Soucy J-P, Chabli A, Lavigne G, Montplaisir J. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J Neurol. 2002 Feb;249(2):164–70.

80. Trenkwalder C, Walters AS, Hening WA, Chokroverty S, Antonini A, Dhawan V, et al. Positron emission tomographic studies in restless legs syndrome. Mov Disord Off J Mov Disord Soc. 1999 Jan;14(1):141–5.

81. Ryu JH, Lee MS, Baik JS. Sonographic abnormalities in idiopathic restless legs syndrome (RLS) and RLS in Parkinson's disease. Parkinsonism Relat Disord. 2011 Mar;17(3):201–3.

82. Kwon D-Y, Seo W-K, Yoon H-K, Park M-H, Koh S-B, Park K-W. Transcranial brain sonography in Parkinson's disease with restless legs syndrome. Mov Disord Off J Mov Disord Soc. 2010 Jul 30;25(10):1373–8.

83. Kedia S, Moro E, Tagliati M, Lang AE, Kumar R. Emergence of restless legs syndrome during subthalamic stimulation for Parkinson disease. Neurology. 2004 Dec 28;63(12):2410–2.

84. Chahine LM, Ahmed A, Sun Z. Effects of STN DBS for Parkinson's disease on restless legs syndrome and other sleep-related measures. Parkinsonism Relat Disord. 2011 Mar;17(3):208–11.

85. Riley DE, Lang AE. The spectrum of levodopa-related fluctuations in Parkinson's disease. Neurology. 1993 Aug;43(8):1459–64.

86. Oshiro S, Morioka MS, Kikuchi M. Dysregulation of iron metabolism in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Adv Pharmacol Sci. 2011;2011:378278.

87. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep. 1998 Jun 15;21(4):371–7.

88. Allen RP, Barker PB, Wehrl FW, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology. 2001 Jan 23;56(2):263–5.

89. Schmidauer C, Sojer M, Seppi K, Stockner H, Högl B, Biedermann B, et al. Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. Ann Neurol. 2005 Oct;58(4):630–4.

90. Srivanitchapoom P, Pandey S, Hallett M. Restless legs syndrome and pregnancy: a review. Parkinsonism Relat Disord. 2014 Jul;20(7):716–22.

91. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, et al. Restless legs syndrome and pregnancy. Neurology. 2004 Sep 28;63(6):1065–9.

92. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med. 2004 Jan 26;164(2):196–202.

93. Dzaja A, Wehrle R, Lancel M, Pollmächer T. Elevated estradiol plasma levels in women with restless legs during pregnancy. Sleep. 2009 Feb;32(2):169–74.

94. Tunç T, Karadağ YS, Doğulu F, Inan LE. Predisposing factors of restless legs syndrome in pregnancy. Mov Disord Off J Mov Disord Soc. 2007 Apr 15;22(5):627–31.

95. Becker JB. Direct effect of 17 beta-estradiol on striatum: sex differences in dopamine release. Synap N Y N. 1990;5(2):157–64.

96. Pereira JC, Pradella-Hallinan M, Lins Pessoa H de. Imbalance between thyroid hormones and the dopaminergic system might be central to the pathophysiology of restless legs syndrome: a hypothesis. Clin Sao Paulo Braz. 2010 May;65(5):548–54.

97. Kaufman S. Some metabolic relationships between biopterin and folate: implications for the 'methyl trap hypothesis'. Neurochem Res. 1991 Sep;16(9):1031–6.

98. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Mollica G, et al. Pregnancy as a risk factor for restless legs syndrome. Sleep Med. 2004 May;5(3):305–8.

99. Walters AS, Wagner M, Hening WA. Periodic limb movements as the initial manifestation of restless legs syndrome triggered by lumbosacral radiculopathy. Sleep. 1996 Dec;19(10):825–6.

100. Zobeiri M, Shokoohi A. Restless leg syndrome in diabetics compared with normal controls. Sleep Disord. 2014;2014:871751.

101. Guo S, Huang J, Jiang H, Han C, Li J, Xu X, et al. Restless Legs Syndrome: From Pathophysiology to Clinical Diagnosis and Management. Front Aging Neurosci. 2017;9:171.

102. Gemignani F, Melli G, Alfieri S, Inglese C, Marbini A. Sensory manifestations in Charcot-Marie-Tooth disease. J Peripher Nerv Syst JPNS. 2004 Mar;9(1):7–14.

103. Luigetti M, Del Grande A, Testani E, Bisogni G, Losurdo A, Giannantoni NM, et al. Restless leg syndrome in different types of demyelinating neuropathies: a single-center pilot study. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 2013 Sep 15;9(9):945–9.

104. Cotter PE, O'Keeffe ST. Restless leg syndrome: is it a real problem? Ther Clin Risk Manag. 2006 Dec;2(4):465–75.

105. Hogl B, Frauscher B, Seppi K, Ulmer H, Poewe W. Transient restless legs syndrome after spinal anesthesia: A prospective study. Neurology. 2002 Dec 10;59(11):1705–7.

106. Viola-Saltzman M, Watson NF, Bogart A, Goldberg J, Buchwald D. High prevalence of restless legs syndrome among patients with fibromyalgia: a controlled cross-sectional study. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 2010 Oct 15;6(5):423–7.

107. Manconi M, Fabbrini M, Bonanni E, Filippi M, Rocca M, Murri L, et al. High prevalence of restless legs syndrome in multiple sclerosis. Eur J Neurol. 2007 May;14(5):534–9.

108. Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: A systematic review and new concept. Neurology. 2016 Apr 5;86(14):1336–43.

109. Abele M, Bürk K, Laccone F, Dichgans J, Klockgether T. Restless legs syndrome in spinocerebellar ataxia types 1, 2, and 3. J Neurol. 2001 Apr;248(4):311–4.

110. Tan E-K. Association of familial ataxia and restless legs syndrome. J Neuropsychiatry Clin Neurosci. 2007;19(2):204–5.

111. Ondo WG, Lai D. Association between restless legs syndrome and essential tremor: Association between RLS and Essential Tremor. Mov Disord. 2006 Apr;21(4):515–8.

112. Walters AS, Moussouttas M, Siddiqui F, Silveira DC, Fuentes K, Wang L, et al. Prevalence of stroke in Restless Legs Syndrome: Initial Results Point to the Need for More Sophisticated Studies. Open Neurol J. 2010 Jun 15;4:73–7.

113. Erden EC, Erden İ, Türker Y, Sivri N, Dikici S, Ozşahin M. Incremental effects of restless legs syndrome on nocturnal blood pressure in hypertensive patients and normotensive individuals. Blood Press Monit. 2012 Dec;17(6):231–4.

114. Erden İ, Çakcak Erden E, Durmuş H, Tıbıllı H, Tabakçı M, Kalkan ME, et al. Association between restless leg syndrom and slow coronary flow. Anadolu Kardiyol Derg AKD Anatol J Cardiol. 2014 Nov;14(7):612–6.

115. Lespérance P, Djerroud N, Diaz Anzaldua A, Rouleau GA, Chouinard S, Richer F, et al. Restless legs in Tourette syndrome. Mov Disord Off J Mov Disord Soc. 2004 Sep;19(9):1084–7.

116. Lakshminarayanan S, Paramasivan KD, Walters AS, Wagner ML, Patel S, Passi V. Clinically significant but unsuspected restless legs syndrome in patients with sleep apnea. Mov Disord Off J Mov Disord Soc. 2005 Apr;20(4):501–3.

117. Sperfeld A-D, Unrath A, Kassubek J. Restless legs syndrome in hereditary spastic paraparesis. Eur Neurol. 2007;57(1):31–5.

## Biography

Ryan Murray Walker grew up in the small seaside village of Kommetjie in Cape Town, South Africa. Only towards the end of his schooling career did Ryan decide that medicine was what he wanted to pursue. It happened when he was one of the first on-scene at a great white shark attack on a local beach. From then on Ryan was committed to achieving his new-found passion in medicine. Ryan then completed a paramedics course, and enrolled in a BSc Human Life Science programme before transferring to Croatia to study medicine.

In his free time, Ryan loves spending time with his family and has a passion for collecting and restoring classical cars. He is also the owner of two dachshunds and a Danish pointer-cross that he adopted during his time spent in Croatia. If you cannot find him, he is most probably in the garage tinkering with a car or taking his dogs on a stroll around his village.