QUALITIES OF RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS

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DECLARATION

This thesis is submitted in the optional format, approved by the faculty, of published work with supporting introductions, as literature reviews, and conclusion.

I declare that the work contained in this thesis is my own, unless otherwise acknowledged.

This work has not been submitted before for any degree or examination at any other university.

Signed on the _____ day of _____, 2007.

ABSTRACT

The two disorders of Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLM) are well recognised as fairly common neurological disorders. The presentation is of a sensory and motor component suggestive of a state of hyperexcitability of the nervous system. The underlying abnormality is believed to involve a dopamine deficiency but many of characteristics of the disorders have not been adequately described or quantified. I investigated, firstly, the possible reasons for the gender bias in the prevalence studies and found that women were more likely to have some associated conditions which may be related to RLS as well as a higher symptom load when compared to men subjects with RLS. I then looked at the problems of analysing the sensations occurring in RLS. Due to the lack of an adequate measuring tool and the possibility of a relationship between the sensations of RLS and those of pain, I used a validated descriptive pain questionnaire (the McGill pain questionnaire) to measure the sensations of RLS. Subjects with RLS were able to describe the sensations with the pain questionnaire and severity indices calculated from the McGill correlated well with measures of RLS severity but not with other intensity measures for pain. In the area of motor events I investigated the possibility of creating a classification system for the muscle activations documented as PLM. I recorded multiple muscle groups in the legs during sleep and devised a classification using sequence of activation and timing of activations from the different muscles. I also used the classification to show subtle changes in the leg activation patterns associated with change in sleep stage.

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PREFACE

This thesis is divided into nine chapters**. Chapter 1** provides a general background to the disorders of Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLM). **Chapter 2** introduces the aims of the thesis based on that preview.

Chapters 3 and 4 are concerned with the gender bias, in favour of women, found in all prevalence studies of RLS in various populations. Chapter 3 provides a literature review to introduce the topic and suggest some explanations and theories for this gender bias. Chapter 4 contains the paper published on genetic differences in a South Africa population investigating some of the theories from chapter 3.

Chapter 5 introduces the concept of hyperexcitability of the nervous system and the generation of both exaggerated and spontaneous phenomena both in the sensory and motor system. The relationship of these phenomena to those sensory phenomena of RLS and the motor phenomena of PLM is then discussed. The issue of measuring tools for spontaneous sensory and motor phenomena is considered. **Chapter 6 and 7** contain 1 published paper (Chapter 6) and one submitted paper (Chapter 7) looking at potential new measuring tools for the sensory phenomena (Chapter 6) and motor phenomena (Chapter 7).

Finally, in **Chapter 8** the results are summarised and ideas for new directions in research advanced. The references in **Chapter 9** are those used for all literature reviews.

CHAPTER 1

INTRODUCTION

Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLM) are related neurological disorders characterised by spontaneous activity in both the sensory and motor systems summarized by the sufferer (or bedpartner) as “restlessness”. The sensory component occurs as RLS with an unpleasant, uncomfortable feeling in the legs urging the sufferer to move in order to relieve the sensation. The motor restlessness presents as PLM, which are involuntary repetitive activations in the muscles of the legs occurring during sleep and/or wakefulness. While often occurring together in the same patient, the disorders may be independent of each other.

1.1 Restless Legs Syndrome

The history of RLS begins in the seventeenth century with a description from Dr T Willis in 1685 of a patient who had difficulty sleeping due to discomfort in the limbs (Coccagna et al. 2004). For many years, in the absence of any physical deformity or obvious pathophysiology, RLS was considered to be psychological in origin, as a form of “hysteria” or neurosis and in 1861 was named “Anxietas tibiarum” by Wittmaack (Coccagna et al. 2004). Other patients were reported subsequently in anecdotal notes but Karl-Axel Ekbom has been credited with the first scientific description of RLS in 500 patients in 1945 (Ekbom 1945). He also coined the term Restless Legs Syndrome (RLS) but for many years after that, particularly in Europe, the disorder was referred to as Ekbom’s syndrome. Doubt has been cast on the specificity of these early diagnoses because of the subsequent description of many similar sensory disorders which are now distinguished from RLS by refined diagnostic criteria.

1.1.1 Definitions and diagnosis

RLS is a spontaneous sensory disorder, diagnosed on the description of a very specific sensory phenomenon. The diagnostic criteria for RLS are defined by positive answers to four questions asked of patients which were validated by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 (Walters 1995) and further refined by an NIH committee in 2003 (Allen et al. 2003). The current diagnostic questions for RLS are:

1. Do you have an urge to move your legs usually accompanied or caused by uncomfortable and unpleasant sensation in the legs?
2. Does the urge to move or unpleasant sensation begin or worsen during periods of rest or inactivity such as lying or sitting?
3. Is the urge to move or unpleasant sensation partially or totally relieved by movement, such as walking or stretching?
4. Is the urge to move or unpleasant sensation worse in the evening or night than during the day?

An answer in the affirmative to all four of these questions would confirm the presence of RLS. Negative answers to one or more of these questions have been shown to distinguish RLS from similar disorders such as akathisia (Walters et al. 1991) and painful legs and moving toes (Sanders et al. 1999).

While the four questions are diagnostic in their own right there are other associated features according to the NIH document (Allen et al. 2003) which are considered to confirm the diagnosis of RLS. These are:

A positive family history: Between 40 and 90% of patients in studies are aware of family members who also suffer from the disorder (Barriere et al. 2005; Winkelmann and Ferini-Strambi 2006). First degree relatives have a 3.3 fold increase in incidence of RLS symptoms (Hening et al 2004a) when compared to control populations. There are however, a significant number of patients with RLS who have no family history so a lack of family history is not specific.

Positive response to dopaminergic therapy: Resolution of the symptoms with dopamine replacement first was described in 1982 (Akpinar 1982). Since then, treatment with either L-Dopa, combined with carbidopa, or dopamine agonists has been shown to be highly effective in treating the condition such that these agents are now considered to be first-line therapy for patients who complain of the RLS sensations (Stiasny et al. 2002; Hening et al 2004b). The response to supplemental dopamine is fairly specific to RLS and improvement of the sensory disorder following a short course of dopamine replacement may confirm the diagnosis of RLS.

This positive response to dopamine therapy has driven a number of research projects looking at imaging studies, autopsy studies and measurement of dopamine analogues and breakdown products in the cerebrospinal fluid, the specifics of which are beyond this

brief review. Although there are changes in dopamine synthesis, secretion and receptor types in patients with RLS, the lack of consistency makes the results difficult to formulate into a tight hypothesis. Nevertheless, the significant response of RLS to dopamine replacement therapy has convinced most researchers to consider the cause of RLS and PLM to be an abnormality in the dopaminergic pathways in the brain (Montplaisir et al 2000; Allen 2004; Trenkwalder and Paulus 2004; Barriere et al 2005).

Periodic limb movements (PLM): These spontaneous motor events typically are described as dorsiflexion of the big toe and ankle, sometimes extending to a spreading movement of the toes with flexion of the knee and hip (Coleman et al. 1980). While PLM were initially described as an independent condition, they were found to occur in pathological numbers in up to 84% of patients with RLS (Michaud et al. 2002). Increasing severity of RLS also correlates significantly with increasing numbers of PLM during sleep (Allen and Earley 2001b; Garcia-Borreguero et al 2004). The link between RLS and PLM is strengthened further by the finding that spontaneous periodic movements similar to those occurring during sleep also occur during wakefulness in patients with RLS, particularly when they are asked to refrain from moving during the sensory disturbance (Montplaisir et al. 1998). A recent letter has suggested that these movements during wakefulness should be used as a diagnostic criteria for RLS (Michaud 2006).

1.1.2 Prevalence

Most population based studies on RLS would confirm that it affects enough people to be a clinically significant disorder (Garcia-Borreguera 2006). However, the prevalence of RLS varies according to the country surveyed and the questions asked. The two extremes of prevalence are: less than 2% in Japan and Singapore (Kagayama et al 2000; Tan et al. 2001) to 11.5% in Scandinavia (Bjorvatn et al. 2005) suggesting a significant difference in prevalence between Western and Eastern populations. However, comparing prevalence data from different countries is difficult due to procedural discrepancies. Diagnosis of RLS in some older prevalence studies relied on a single question, often including the presence of a sleep disturbance as a diagnostic criterion, which no longer would be acceptable (Lavigne and Montplaisir 1994; Phillips et al. 2000). There are also problems in comparing studies when the definition of "significant RLS", determined by the number of days the subjects are affected by the sensations, varies between studies. Despite these difficulties it is generally accepted that approximately 10% in European and American populations will fulfil the diagnostic criteria of RLS.

The prevalence of RLS is increased in subsets of the normal population specifically in pregnant women (26% Manconi et al. 2004), and in patients with co-morbidities such as renal failure (20% Winkelmann et al. 1996), and iron deficiency (O'Keeffe et al. 1994). RLS in these, and other less common conditions, comprises so-called "secondary RLS" which may resolve once the primary condition has resolved, by birth of the child

(Manconi et al. 2004), replacement of iron (Kryger et al. 2002) or transplantation in the case of end-stage renal disease (Winkelmann et al. 2002b).

1.2. Periodic Limb Movements

Motor activity related to RLS, as involuntary movements of the lower limbs while the sensation was present during wakefulness, were first noted in 1943 by Allison (Allison 1943 cited in Coccagna et al. 2004).

In 1953 the presence of involuntary leg movements during sleep, then called nocturnal myoclonus, was reported by Symonds who, due to technical limitations, wrongly diagnosed them as a form of epilepsy (Symonds 1953). The first group to record these movements formally during the night was led by Lugaresi. He published various papers outlining the phenomenon, particularly its common occurrence in RLS (Lugaresi et al. 1965), but also as an isolated phenomenon (Lugaresi et al. 1966).

1.2.1 Definition and diagnosis

In 1980 Coleman disagreed with the term myoclonus as the leg movements that he had now formally described and characterized as occurring in the anterior tibialis muscle, were too short and repetitive to fit the definition of myoclonus: he called them Periodic Limb Movements (PLM) (Coleman et al. 1980). When the PLM occur during sleep they are referred to as PLMS and when they occur during wakefulness they are referred to as

PLMW. A third term, PLM disorder (PLMD), is used to define a syndrome where the presence of the leg movements can be shown to cause a sleep disorder and thus have a clinical impact. The relevance of PLM to sleep disorders has, however, been a subject of debate with some authors disputing that PLM alone cause any sleep disruption (Mendelson 1996; Mahowald 2001).

Despite the use of the term “periodic limb movements” the motor events are defined by electrical activations of the muscle anterior tibialis recorded on electromyography (EMG). In this review, the term periodic limb movement is used to indicate these electrical activations, as is done routinely. Whether an EMG activation occurring during sleep fits the criteria for inclusion as a periodic limb movement depends on the fulfilment of scoring criteria based on those first proposed in 1982 (Coleman 1982), refined and accepted by the American Sleep Disorder Association (The ASDA Atlas Task Force 1993) and again updated in 2006 in a document approved by the World Association of Sleep Medicine (WASM) (Zucconi et al. 2006). The current (WASM) criteria defining pathological leg movements involve the identification of a PLM sequence consisting of EMG activations which fulfil the following criteria:

1. There is an increase in EMG amplitude of at least 8uV above baseline
2. The individual burst duration lasts from 0.5 to 10 seconds
3. The EMG activations are separated by at least 5 and not more than 90 seconds.
4. There are four or more EMG bursts fulfilling these criteria.

The significance of the specific amplitude and duration criteria for the PLM has not been objectively established as highlighted in a recent review (Hornyak 2006). One recent paper has formally questioned the legitimacy of the current amplitude criteria as producing an underestimation in the number of PLM counted during sleep (Gschliesser et al. 2006). Whether this underestimation is important is unclear. The time intervals between activations have been based on more objective data. One of the first research papers describing PLM reported that there was a clear peak in the inter-movement intervals between 20-40 seconds with the remainder of the EMG activations scattered on either side of this peak (Coleman 1982). The dominance of the 20 to 40 second inter-movement interval has been confirmed more recently using computerized analysis (Ferri, Zucconi et al. 2005). However, despite much research neither the significance nor origin of these specific time intervals have been established. The lack of clarity associated with discriminating pathological from non-pathological PLM has created a secondary problem: defining the prevalence of the phenomenon and thus the disorder.

1.2.2 Prevalence

The muscle activations which define PLM are usually detected on overnight sleep recordings for other sleep disorders although a history from the bed partner of limb movements during sleep in the subject has also been used for determining prevalence. The largest general population study using a personal history of leg movements during sleep was done in 18 980 subjects using the International Classification of Sleep Disorders criteria (ICSD) and reported the presence of PLMD in 3.9% of the population

(ICSD 1990; Ohayon and Roth 2002). While pathological levels of PLM are found in most patients complaining of RLS, PLM are often found associated with other sleep disorders (Lesage and Hening 2004). Pathological PLM, as defined by an PLM index >5 per hour, are found in a greater proportion of patients with narcolepsy (Montplaisir and Godbout 1986), obstructive sleep apnoea (Warnes et al. 1993) and REM behaviour disorder (Schenck and Mahowald 1990) than in normal controls. Another study comparing different groups of people found a prevalence of PLM greater than 5 per hour of sleep in 30% of patients with hypersomnia, 40% of patients with insomnia and 55% of control subjects in a small sample (Montplaisir et al. 2000). Patients with narcolepsy and RLS had a prevalence of 80 and 85% respectively. In a survey of elderly subjects, who were normal sleepers, between 30% and 50% were found to have PLM indices greater than 5 per hour (Ancoli-Israel et al. 1985; Dickel and Mosko 1990). Thus a PLM index greater than 5 per hour did not necessarily separate patients with frank sleep pathology from normal controls and was not associated with any particular type of sleep disorder. Therefore, the significance of pathological numbers of PLM, which fulfil the scoring criteria, when discovered on a routine overnight sleep recording is unclear at this point.

1.3. Restless Legs Syndrome and Periodic Limb Movements as one disorder

One confounder to any discussion of the origins of RLS and PLM is whether the sensory and motor events comprise one or two separate disorders. There is good evidence that they are in fact one disorder, the two components of which may also occur independently of each other in some cases.

While patients with isolated RLS and PLM have been described, the high numbers of patients with RLS also having PLM (80%) would suggest a common site of origin for the sensory symptoms and motor events. The presence of PLMW, with similar characteristics to PLMS, during wakefulness in patients with RLS provides additional evidence for this common neurophysiological link (Montplaisir et al. 1998; Michaud et al. 2001). The movements during wakefulness are reported anecdotally by patients but are made more prominent by the Suggested Immobilization Test (SIT). This test asks sufferers not to move their legs when they feel the restlessness but rather to hold them still while the activity of the anterior tibialis muscle is recorded with electromyography (EMG) (Michaud et al. 2002). A number of studies have now shown a significant correlation between the severity of the RLS sensations, the PLMW index obtained on a SIT test and the number of PLMS observed in a subsequent night of sleep (Montplaisir et al. 1998; Allen and Earley 2001b; Garcia-Borreguero et al 2004; Aksu et al 2006). More detailed analysis of the movements may strengthen the link between the awake and sleep motor phenomena confirming the one site theory.

It is important to confirm whether the two disorders are connected by a similar pathophysiological site as information gained in the analysis of the sensations of RLS may then be used to explain the PLM and vice versa. When two components of one disorder are each restricted to either wakefulness or sleep, information gained from techniques which are restricted to one particular phase, such as imaging techniques during wakefulness, can be used to explain both disorders.

CHAPTER 2

AIMS OF THESIS

There is good evidence that a central deficiency of the neurotransmitter dopamine is the underlying cause of the symptoms of Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLMs). There are, however, many fundamental questions related to the two disorders which cannot at present be answered. My thesis therefore aimed to investigate three different areas related to RLS and PLM.

One striking characteristic of RLS is the higher prevalence of RLS in the female gender in all population studies. Despite this, no work has been done to investigate the mechanisms producing this phenomenon. For my first study I asked a population of subjects who had contacted me in response to an advert for a treatment study to complete a questionnaire in order to define some aspects of the gender bias. In particular I was interested in the genetic transmission, thus asking about family history, as well as the impact that the sensations and motor events of RLS had on sleep. The relationship between the RLS and other medical disorders was also investigated.

The second and third studies focussed on the problems with measuring and defining the sensory and motor events associated with the two conditions. My second study was inspired by one of the possible reasons for the gender bias - defining the sensations of RLS. By adequate descriptions of the sensations of RLS the origin of the sensations may be uncovered. Of particular interest is the relationship of the RLS sensations to those of pain – given the well-known gender bias favouring a lowered pain threshold in women. A significant proportion of patients with RLS remark that the sensations are in fact painful and thus using a measuring tool usually reserved for pain may be useful to define the type

of sensation occurring in Restless Legs Syndrome. The requirement to be able to analyse both qualitative and quantitative features of this sensation as well as the difficulty that most patients have in describing the sensation led me to the McGill Pain Questionnaire (MPQ) (Melzack, 1975). The MPQ has been used extensively and well-validated in the past to define and compare various painful sensations. The aim of my project was to firstly describe the sensations of RLS by means of the descriptive word list in the MPQ and then to compare severity results from the MPQ with severity results from specific RLS related questionnaires.

I then turned to the problem with the measurement of the motor events known as Periodic Limb Movements (PLMs). It is my belief that part of the reason for the dilemma regarding the source and clinical relevance of these muscle activations is due to the lack of a good tool for analyzing the complexity of the leg movements. While three studies have looked at multiple muscle recordings none of them presented a clear reproducible way of analyzing the results (Provini et al.2001, de Weerd et al 2005, Trenkwalder et al 1996a). The aim of my third study was to develop a classification for motor patterns occurring during sleep and for this purpose I recorded the EMG patterns of four muscle groups in each leg on 10 subjects with RLS during sleep. I then applied the classification system in order to analyse how the activation patterns were affected by different sleep stages.

CHAPTER 3

LITERATURE REVIEW: WHY THE GENDER DIFFERENCE IN PREVALENCE OF RESTLESS LEGS SYNDROME?

One of the fascinating and under-researched areas in restless legs syndrome (RLS) is the origins of the gender differences in the presentation of the disorder. As discussed previously the prevalence of RLS appears to vary in different populations and, in most of the populations studied, women are more likely to be affected by the condition than are men (Table 1). The reasons for this female preponderance in prevalence studies of RLS, both in general populations as well as those in primary health care, are unknown. When considering the gender bias it may be useful to divide the possible causes into reasons for more women to have the condition and reasons for more women to report the condition, when compared to men.

3.1. Do more women have Restless Legs Syndrome?

A gender bias in the presence of RLS in population groups implies an increase of RLS in the female gender in both primary and secondary RLS. An increase in primary RLS would imply that there is a simple genetic bias producing more women with primary RLS while an increase in the prevalence of secondary RLS implies that women are more likely to have the recognised causes of secondary RLS when compared to men. A third cause of the gender bias in the prevalence of RLS may be a relationship between RLS and other co-morbid disorders which themselves have a gender bias but are, as yet, not considered to be secondary causes of RLS.

Reference	Country(ies)	Subject numbers	Age (y)	Diagnostic criteria	RLS prevalence (%)	female: male
General Populations						
Lavigne (1994)	Canada	2 019	>18	1 question	15	1.31
Phillips (2000)	USA	1 803	> 18	1 question	10	Equal
Ulfberg (2001a,b)	Sweden	2808	18-64	IRLSSG	6.1	1.90
Ohayon (2002)	UK, Germany, Italy, Spain, Portugal	18 980	>15	ICSD	5.5	1.97
Sevim (2003)	Turkey	3234	>18	IRLSSG	3.2	1.56
Berger (2004)	Germany	4 310	>20	IRLSSG	10.6	1.76
Tison (2004)	France	10 263	>18	IRLSSG	8.5	1.81
Bjorvatn (2005)	Norway, Denmark	2 005	> 18	IRLSSG	11.5	1.43
Allen (2005)	USA, Europe	15 391	> 18	IRLSSG	7.2	1.67
Mizuno (2005a)	Japan	3287	>65		1.06	2.43
Primary health care populations						
Rothdach (2000)	Germany	369	65-83	IRLSSG	9.8	2.28
Nichols (2003)	USA	2 099	> 18	IRLSSG	24	1.37
Rijsman (2004)	Netherlands	1 485	50	leg movements	7.1	1.2
Hening (2004a)	USA, UK, France, Spain, Germany	23 052	adults	IRLSSG	9.6	2.18

Table 1. Prevalence studies in general populations and primary health care populations that have reported on gender differences in RLS/PLM. IRLSSG = International Restless Legs Syndrome Study Group. Some gender data recalculated from percentage data given in studies.

3.1.1. Primary RLS – a straight forward genotypic or phenotypic bias.

The only way that genetic transmission can account for a female gender bias in RLS prevalence is if the disorder was transmitted in a way favouring women, possibly sex-linked. There is, however, no linkage study published that will support this hypothesis.

There is clear evidence that RLS is more likely to be transmitted within families and thus has some genetic component (Stiasny et al. 2002; Barriere et al. 2005). Common linkages within different families to chromosome 21q in Canada, 14q in Italy and 9p in the USA show the inheritability traits (Bonati et al. 2003; Desautels et al. 2005; Chen et al 2004). Only a few studies on inheritance patterns, and none of the linkage studies, have included data on gender differences.

In the five family pedigrees analysed by Lazzarini et al (Lazzarini et al. 1999) there was a ratio of 1.4 to 1 preponderance of women sufferers. In their study, however, they excluded those women who had RLS only during pregnancy. Thus, the reported female dominance would increase if these women were included as there would be no similar reason for such an increase in RLS in the male population. Most of the other genetic studies do not indicate gender differences except to say that the inheritance is not sex-linked but rather autosomally linked in families with a strong family history (Winkelmann et al. 2002a). The type of transmission appears to be dominant possibly as a single gene with either a multifactorial component (Winkelmann et al 2002a), age-dependent penetrance (Trenkwalder et al. 1996) or simply highly (between 86 and 100%)

penetrant (Lazzarini et al. 1999; Winkelman and Ferini-Strambi 2006). A susceptibility, only in women with RLS, has been shown in polymorphisms in genes coding for mono-amine-oxidase activity (Desautels et al 2002). This enzyme is involved in breakdown of dopamine in the nervous system and may thus increase the likelihood of RLS in women. However, this subtle evidence, which has not been replicated in other studies may not be sufficient to place genetic causes as the primary determinant of the gender bias in prevalence studies.

One problem with using family trees for genetic studies is the varying age of respondents at the time when the study is performed. The increasing incidence of RLS with advancing age may bias both the total prevalence data as well as the gender differences (Milligan and Chesson 2002; Hening et al. 2004; Allen 2005). Supposedly unaffected younger members in the family tree at the time of study may present with RLS when older particularly after experiencing an unrelated precipitating event, such as pregnancy, with an inherent gender bias known to be linked to RLS. These gender skewed precipitating events may then increase the prevalence in women in the older section of the population but also increase the prevalence of non-familial cases of RLS.

The genetic basis for the higher prevalence of RLS in women may be related to fluxes in gonadal hormones, such as oestrogen and progesterone, particularly the rhythmical changes with menstruation, pregnancy and the gradual decrease in hormonal levels with menopause. These two hormones have myriad effects directly affecting brain function which may affect the likelihood of presenting with RLS. There is a particular relationship

between oestrogen and dopamine. Oestrogen or oestrogen replacement therapy may be protective to the brain in other dopamine related disorders such as Parkinson's and attention deficit disorder (Saunders-Pullman et al 1999). More specifically, oestrogen withdrawal causes loss of dopaminergic cells in the substantia nigra and oestrogen replacement therapy brings about restoration of striatal dopaminergic function in previously oestrogen depleted rats (Lernath et al 2000; Ohtani et al 2001). The protective effects of oestrogen are present in mesencephalic dopaminergic neurones as well which have been suggested to be the dopmainergic neurons affected in RLS (Sawada and Shimohama 2000). This neuroprotective view has not been found consistently in all studies. In fact a higher risk of Parkinson's disease in women taking post menopausal hormone replacement therapy has also been reported (Popat et al 2005). The general conclusion seems to be that women with Parkinson's disease may continue taking hormone replacement therapy. Finally, the normal reduction in dopaminergic neurones that occurs with increasing age is more severe in women when compared to men (Wong et al 1988). Thus the lowered levels of oestrogen and progesterone occurring after menopause may explain the increasing prevalence in the older woman.

The gender differences, in genetic status, dopamine function and oestrogen levels with advancing age, may be enhanced by a number of secondary causes of RLS which appear to produce iron deficiency which may also have a gender bias.

3.1.2 Secondary RLS – the role of iron deficiency.

Various independent life events or medical disorders show a higher prevalence of RLS in patients or subjects affected by such events when compared to the general population. Such life events or medical disorders may themselves produce a gender bias in the presentation of RLS. The three recognised secondary causes of RLS are pregnancy, end-stage renal disease and iron deficiency itself – which is presumed to be the underlying mechanism behind the increase in RLS prevalence in all three disorders.

The evidence for an increased prevalence of RLS during pregnancy is accumulating and obviously the gender bias is absolute. The incidence of RLS during pregnancy increases reaching 23-26% by the third trimester (Lee et al. 2001; Manconi et al. 2004). The prevalence of RLS in women also increases with increasing number of pregnancies (increasing parity) (Berger et al. 2004). In this study women of all ages who had never been pregnant (nulliparous) had a prevalence of RLS similar to that of men at similar ages. In most cases of RLS during pregnancy, however, the RLS tends to resolve either towards the end of the pregnancy or after the birth of the child which makes it difficult to explain the long term increase in RLS with pregnancy (Manconi et al 2004). It is possible that pregnancy is the precipitating factor for RLS which then makes the woman more susceptible to RLS caused by other life events after the pregnancy (see below).

The sudden resolution of RLS after parturition also does not fit with the suggestion that the common underlying mechanism for the secondary causes of RLS is that of iron deficiency. A more logical explanation is one with a hormonal basis. Any impact of the hormonal changes specific to pregnancy, including those of oestrogen, progesterone and prolactin, on RLS has not been sufficiently investigated. The high levels of oestrogen and progesterone during pregnancy are unlikely to cause an increase in RLS as a significant decrease in these hormones after menopause is associated with an increase risk of RLS, as discussed earlier (Barriere et al 2005). Also a raised oestrogen level in post menopausal women raises dopamine responsivity when tested by an apomorphine challenge (Craig et al 2004). Possibly other hormones such as oxytocin and prolactin , also associated with pregnancy, are better candidates for the changes in RLS during pregnancy.

The relationship between prolactin and RLS is interesting given the inhibitory effect of dopamine on the secretion of prolactin. The rising prolactin levels during pregnancy may thus be due to a gradual decrease in dopamine levels which would also lead to presentation of RLS symptoms. Prolactin secretion, measured in men with RLS, while following the same diurnal pattern as the symptoms of RLS was not found to differ between men with RLS compared to control men (Wetter et al 2002). The roles of oxytocin, prolactin and thyroid hormones which can all change significantly post-partum, and fluctuate depending on whether the mother breastfeeds or not, are unstudied in the pathogenesis of RLS related to pregnancy (Hendricks et al 1998). The relationship

between the hormonal changes occurring during and after pregnancy and the possible association with depression (see below) have also not been explored.

The prevalence of RLS is also found to be higher in patients with end-stage renal disease. The gender bias of RLS found in general population studies is not found in patients with renal disease who also have RLS. (Gigli et al 2004). There is also no gender bias favouring women in the occurrence or progression of renal disease to end-stage failure (Silbiger and Neugarten 2003; Seliger et al 2001). The association between RLS and iron deficiency in end-stage renal disease is less definite with both positive and negative findings thus implying, in at least some patients with RLS due to renal disease, a different pathophysiology to that of primary RLS (Gigli et al 2004).

The final accepted secondary cause of RLS is that of iron deficiency itself. Biological markers of iron deficiency include a lowered serum ferritin, a measure of iron storage, a lower haemoglobin and a raised tranferrin level (Fleming and Menendez 2004). Iron deficiency has been shown in RLS patients using a variety of measures for iron status including serum ferritin, cerebrospinal levels of ferritin and transferrin, imaging of regional brain iron status and autopsy measures of brain iron concentrations (Allen et al 2001; Allen 2004; Mizuno et al 2005b). Treatment of the iron deficiency has, in some studies, resulted in resolution of the RLS symptoms (Earley et al 2004; Kryger et al 2002). The relationship between iron deficiency and RLS is presumed to be the requirement for iron as a cofactor for optimal activity of tyrosine hydroxylase, an essential enzyme in the production of dopamine. The connection between a reduction in

dopamine and the presence of RLS has been mentioned before. The most important feature of iron deficiency as far as the gender bias in RLS is concerned is that iron deficiency, within the general population, is more common in women than in men, thus paralleling the gender bias of RLS symptoms (Rushton et al 2001).

Thus as far as the secondary causes of RLS are concerned a variety of mechanisms, including hormonal fluctuations, iron deficiency and possibly some additional unknown variables may occur together to increase the number of women afflicted by the secondary causes of RLS.

3.1.3 Co-morbid factors – gender biased medical disorders.

The gender bias seen in prevalence studies of RLS may also be affected by co-morbid medical disorders which are not currently considered as secondary causes of RLS but may play some part in the gender bias. A number of medical disorders occur with an increased prevalence in patients with RLS, when compared to controls, including arthritis, obesity, respiratory diseases, hypothyroidism, depression and anxiety, and possibly hypertension (Banno et al. 2000; Ulfberg et al. 2001a,b; Hening et al. 2004a; Sevim et al. 2004; Winkelmann et al. 2005). In most of these disorders the link to RLS is not immediately obvious and only hypothyroidism, depression and anxiety are known to have an inherent gender bias.

The connection between hypothyroidism and RLS, as far as any gender bias is concerned, appears to be quite strong, as previously diagnosed hypothyroidism was found only in women with RLS and not in men with RLS. RLS and hypothyroidism share a common biochemical link in the amino acid tyrosine as a precursor in the synthesis of dopamine and thyroid hormones. Tyrosine hydroxylase, the enzyme facilitating the transformation of tyrosine to DOPA requires iron as a cofactor and a brain iron deficiency has been found in patients with RLS (Fitzpatrick 1989; Connor et al. 2003; Allen 2004). Hypothyroidism may also be related to a brain iron deficiency as a low thyroid hormone level negatively affects the handling of iron by the brain, at least in developing rats (Levenson and Fitch 2000). Iron deficiency in its turn reduces thyroid peroxidase activity which would then cause lowered thyroid hormone levels (Hess et al. 2002). Thus links between brain iron deficiency and both the dopamine deficiency of RLS and hypothyroidism may explain why hypothyroidism and RLS are likely to occur in the same people (Allen 2004; Zimmermann and Kohrle 2002). An increased risk in women of both iron deficiency and hypothyroidism, independent of RLS, may then increase the prevalence of RLS in this gender (Galofre et al. 1994; Rushton et al. 2001). Despite this attractive hypothesis the potential links between hypothyroidism and RLS, and particularly their impact on gender bias, have not been researched.

The other conditions, with an inherent gender bias, which may impact the prevalence of RLS are depression and anxiety. Women are more likely to suffer from depression and anxiety during their lifetime compared to men (Parker and Hadzi-Pavlovic 2004; Piccinelli and Wilkinson 2000). There is also an increased prevalence of both depression

and anxiety in subjects with RLS, which, when compared to age matched controls, occurs independently of the sampling technique (Sevim et al. 2004; Winkelmann et al. 2005; Saletu et al. 2002).

It is unclear how the relationship or association between RLS and depression and anxiety arises. Patients with RLS may be more likely to develop depression and anxiety due to the impact of RLS on lifestyle and quality of life (Allen et al 2005). Neurotransmitter changes, adverse life events and social norms which increase the relative risk of depression in women may also increase the risk of RLS in women, but are at present unstudied (Piccinelli and Wilkinson 2000). Treatment of the psychiatric complaints may increase the prevalence of RLS because, in some patients, antidepressant medication may induce or aggravate RLS (Dorsey et al. 1996; Brown et al. 2005). Whether the long-term risk of RLS is increased by previous use of antidepressant medication, as may be occurring with pregnancy induced RLS, is unknown. A further link between RLS and depression is the common complaint in both groups of patients when seeking treatment - that of sleep disruption: up to 90% of patients with RLS and 70% of patients with depression and anxiety complain of various types of insomnia (Winkelmann et al. 2000; Allen et al 2005). Long term insomnia, such as could be caused secondarily by RLS, may cause depression even many years after the start of the insomnia complaint (Riemann and Voderholzer 2003). Thus the relationship between these two disorders appears quite complex and may have several origins which have not been defined as yet.

Even if there is an actual increase in the number of women who have RLS, the consequences of RLS may have more impact in women thus increasing the likelihood of women reporting their sensory disturbance.

3.2. Do more women report Restless Legs Syndrome?

The second major reason why there is a gender bias in population studies of RLS may be because women with RLS are more likely to report the disorder. There are two possible reasons for this phenomenon: women may be more sensitive to the impact of RLS on sleep and also to the sensations themselves.

3.2.1 Impact of sensations of RLS on sleep.

The influence of gender on the sleep disturbances occurring in patients with RLS, either on sleep onset or sleep continuity, has not been analysed. However, the impact of RLS on sleep generally is significant. In population-based studies, between 70 and 90% of patients with RLS complain of sleep disruption – either as a sleep-onset or sleep-continuity problem (Winkelmann et al 2000, Allen et al 2005).

The effect of RLS on sleep onset is due partly to the circadian rhythm of RLS sensations, which are uncomfortable and therefore interfere with the onset of sleep, but mainly due to the "urge to move" component inherent in the defining characteristics. The sensations of RLS increase in severity in the evening, when compared to the daytime, particularly

between 17:00 and 01:00 (Hening et al. 1999; Trenkwalder et al. 1999). The inability of the RLS sufferer, when the sensations are present, to lie still and relax will interfere with the ability to fall asleep without difficulty. The continuous movement required to ease the sensory disturbance thus prevents the sufferer from falling asleep. The strong association between RLS and insomnia is shown by a finding where 45% of a group of patients complaining of sleep-onset insomnia were found to have symptoms of RLS (Brown et al. 2005). Involuntary movements while awake may also retard sleep onset as the number of leg movements occurring during wakefulness correlates positively with increasing severity of RLS (Garcia-Borruguero et al 2004). Any gender difference in the circadian variations, the relationship between the sensations and the urge to move or the involuntary movements is unknown.

Between 60 and 85% of RLS sufferers also complain of problems with sleep continuity usually defined as waking, often repetitively, during the night (Winkelmann et al. 2000; Hening et al. 2004a). Often, once woken, the sufferer is unable to go back to sleep due to recurrence of the sensory abnormality. The waking during sleep is presumed to be caused by arousals induced by PLM during sleep and women have a greater number of leg movements during sleep, when compared to men (Montplaisir et al. 1997). The increase in observed PLM in women is not associated, however, with an increase in the complaints of waking during the night. This disassociation between leg movements and symptoms has been found in many studies (Montplaisir et al. 1997; Mendelson 1996; Mahowald 2001). Thus more work is required to determine the relationship between

waking at night and the number of PLM as well as any gender differences in these variables.

The impact of RLS and PLM may be more severe on the sleep of women because of subtle underlying differences in sleep between the genders. Consistent gender differences occur in the variables associated with normal sleep (Manber and Armitage 1999). Adult and adolescent women, when compared to men, are also likely to have up to twice the prevalence of insomnia in prevalence studies of the general population (Camhi et al 2000; Chevalier et al. 1999; Li et al. 2002; Voderholzer et al. 2003). RLS patients are likely to express the same sleep disruptive habits and inability to control pre-sleep thoughts as are patients with primary insomnia (Edinger 2003). Thus if the insomnia seen in RLS has the same origins as primary insomnia, which is itself more prevalent in women, then women with RLS will be more likely to present with insomnia. This may be due to a greater impact of RLS on sleep onset in women but also because, if suffering from insomnia, by spending more time in bed trying to fall asleep women may be more likely to be aware of the RLS sensations.

The gender bias in insomnia may be exacerbated by the gender bias in depression as discussed previously, because women are more likely to present with sleep disturbances when depressed than are men (Pallesen et al. 2001; Silverstein 2002). It is also possible that women are more sensitive to the effects of insomnia, and therefore report more distress when compared to men with insomnia confirmed by the lack of any difference in objective criteria between women and men insomniacs despite more severe subjective

complaints in women (Voderholzer et al. 2003). Women with insomnia also report increased distress when compared to men with similar complaints (Rosenthal et al. 1994). It is not clear, however, whether this increased level of distress is linked to the prevalence of depression and anxiety.

Thus while RLS / PLM and sleep disruption appear to be linked, the exact relationship is unclear and the impact of any gender bias is unexplored. One component of the gender bias in the sleep disruption, particularly at sleep onset, may be due to an increased sensitivity, in women, to the sensations of RLS themselves.

3.2.2 Sensitivity to sensory dysfunction

Sensitivity to a sensory stimulus is usually measured by means of threshold and tolerance and has been most clearly defined in the measurement of pain. The sensory threshold is defined as the minimal intensity of a stimulus required for perception (Kandel et al 2000). There are two distinct components: the capacity of the sensory system to detect the stimulus, which depends on a sufficient intensity of stimulus to produce a train of action potentials in the sensory nerve, and the response criterion, which depends on an individuals personal traits to decide whether a stimulus is present or not (Kandel et al. 2000). Tolerance to a stimulus is the maximum intensity of that stimulus that can be tolerated by an individual. As with sensory threshold, tolerance to a stimulus is also influenced by the individual reaction to the sensation, particularly related to past experiences (Fillingim et al. 1999).

Using these criteria for other, possibly painful, sensory stimuli, in the analysis of the sensations of RLS and pain may be justified as between 40 and 80% of patients with RLS comment that their sensations are sometimes painful (Winkelmann et al. 2000; Allen et al 2005). However, any gender bias related to this perception of pain is unknown. The literature describing the gender difference in sensitivity to noxious stimuli is extensive and appears to show that women are more sensitive to pain than men both in experimental pain settings and medical conditions associated with a variety of chronic pain disorders, such as fibromyalgia (Unruh 1996; Fillingim et al. 1999). A reduced pain tolerance (increased sensitivity) in women is seen for a variety of experimental pain types, such as heat (Feine et al. 1991), electrical (Walker and Carmody 1998) and mechanical stimuli (Sarlani and Greenspan 2002). There is also evidence that much of the gender differences seen in pain perception occurs in the coping strategies used to deal with pain (Keogh and Herdenfeldt 2002). Thus, if the sensations are painful, the same biological intensity of pain may affect women patients with RLS more severely than men with RLS.

Many RLS patients, however, do not complain of painful sensations and studies looking into gender differences in sensory thresholds apart from those of pain show contradictory results. For non-painful stimuli, women were found to have a reduced threshold to warmth in one study (Fillingim et al. 1999), but not in another (Bartlett et al. 1998). No gender difference has been found in vibration thresholds (Meh and Denislic 1995; Lindsell and Griffin 2003). The gender bias is reversed when measuring the pain

response to direct pressure exerted on the ulnar nerve where men subjects were found to be more sensitive than female subjects (Morell et al. 2003). These results identify gender differences linked to specific types of sensation which may be important given the unusual, and as yet undefined, sensations described by patients with RLS.

The patient descriptions of the sensations of restless legs syndrome, as highlighted in the NIH document, appear to be closest to those of paraesthesias or dysaesthesias but no work appears to have been done regarding any gender bias in this type of sensation from other causes apart from neuropathic pain (Bouhassira et al. 2004). Thus whether the sensations are painful or non-painful, a gender bias in the perception of the sensations may increase the impact of the sensations in women, when compared to men.

The sensitivity to sensory stimuli may also change with circadian rhythms which differ according to the type of pain experienced. Of interest is that the pain associated with spinal cord pathology has a similar circadian rhythm to that of the sensations of RLS (Anke et al 1995). The exacerbation of RLS sensations in the evening has been linked to the circadian rhythm of dopamine and the gender differences in dopamine responsiveness (outlined previously) may increase the severity of the sensations in women when compared to men (Allen 2004; Earley et al 2006).

In conclusion, various components of the RLS disorder may produce more common symptoms (in the case of genetic factors and precipitating or co-existing conditions) or more severe symptoms (in the case of sleep disturbance and response to sensations) in

women patients when compared to men. Each one of the factors described above may occur in isolation or in combination. The relative contributions of these various factors to the reported gender bias in RLS have not been studied.

CHAPTER 4

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Gender differences in the presentation of subjects with restless legs syndrome

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Abstract

Background and purpose: To better understand the origin of the disproportionate number of women in previous treatment studies of patients with restless legs syndrome (RLS).

Patients and methods: We conducted a survey in a self-selected group of patients who responded to print and radio recruiting advertisements regarding a clinical trial for RLS. Subjects completed a questionnaire which solicited information on presenting features of RLS, sleep-related symptoms, co-morbidities and family history.

Results: A total of 158 (63% female) subjects with a mean age of 49 (±16) years fulfilled the criteria for putative diagnosis of RLS and participated in the study. There was no gender bias as far as duration of RLS, incidence of family history, number of affected days per week, or severity of daytime sleepiness was concerned. There was a subtle gender bias in sleep-related symptoms (involuntary movements when awake, sleep onset difficulties and frequent wakings at night) where a disproportionately high number of women subjects presented with all three symptoms. For any one symptom, or any pair of symptoms, there were no gender differences. Women also were more likely to present with co-existent hypothyroidism. Both male and female subjects were more likely to recall female relatives affected with RLS.

Conclusions: Gender differences associated with symptom load, co-morbidities of RLS and possible patterns of inheritance may contribute to increased numbers of women presenting for treatment of RLS.

Keywords: Restless legs syndrome; Sleep disorder symptoms; Family history; Gender bias

1. Introduction

Many large cohort studies of subjects presenting for treatment of restless legs syndrome (RLS) have shown a disproportionate number of female subjects [1–3]. While there is a tendency for prevalence studies [4–9] to confirm this tendency, other potential contributors to any gender bias at presentation, if it is valid, have not been adequately explored.

One possible basis for the perceived gender bias is the impact of RLS on sleep. Disturbances in sleep onset and sleep continuity have been a consistent and common finding in RLS subjects [8,10].

The increased impact of RLS on sleep in women may be partly explained by the nature of the sensory symptoms of RLS. The sensations of RLS are characterised by some patients as paraesthesias or frank pain [10,15]. If, as has been previously reported, women have a lower threshold and tolerance to pain [16], as well as being more worried and irritated by clinical pain [17], then women with RLS may be more compromised by the sensations of RLS, have more distress and, by implication, be more likely to present for treatment of RLS.

A greater impact of RLS on sleep may be associated with duration of symptoms. Other authors have noted that many RLS sufferers report worsening of the symptoms over time [9,10]. This may be interpreted as having a gradually increasing impact on sleep and may display a gender bias.

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Consistent gender differences have also been found in the attributes of both normal and abnormal sleep itself [11]. General population studies have indicated that women have about twice the prevalence of insomnia as men have [12,13] and report increased distress when compared to men with similar complaints [14].

Thus, women are more likely to have sleep disruption, and to be more compromised by their insomnia and RLS, than men are. If there is a link between RLS and consequential sleep disorder, disproportionately more women may present for treatment.

A second contribution to the gender bias may be related to co-morbidities of RLS, which have intrinsic gender biases. Common psychological disorders, such as depression or anxiety, which have a higher prevalence in women, may either aggravate the symptoms and distress of RLS [5] or provide a secondary cause for insomnia, so increasing the likelihood of RLS being reported. Patients with RLS are more likely to show depressive and anxiety symptoms [18] than are control subjects, and female RLS patients take more antidepressant medications than do men with RLS [19]. Thus, the impact of RLS on sleep may be increased in women through the presence of a secondary condition with an inherent gender bias.

Patterns of inheritance, as suggested by prevalence data, may provide a third reason for the increased numbers of women in treatment studies. The genetic transmission of RLS may compromise women but available evidence is equivocal. Previous studies have shown a higher female-to-female transmission of the condition [20] but also denied a gender difference in transmission [21] within isolated families. If the transmission of RLS is sex-linked and compromises women then there will be a disproportionate number of women with RLS in the general population thus increasing the likelihood of women presenting for treatment.

In order to further explore any possible gender bias in South African patients we investigated sleep-related symptoms, co-morbidity and family history in subjects who fulfilled the diagnostic criteria for RLS and were sufficiently concerned about their condition to respond to advertisements we placed in lay media, recruiting volunteers for research.

2. Materials and methods

2.1. Subjects

The results are based on analysis of questionnaires completed by subjects who had previously responded to advertisements either printed in a University periodical ($n=13$) or broadcast on a local radio station soliciting volunteers for a clinical trial ($n=145$). The area of reach for both adverts was a multi-cultural, densely populated area of South Africa.

2.2. Questionnaire

Questionnaires were faxed or mailed to respondents, completed and returned. Questionnaires were included in subsequent analysis only if the subject responded in the affirmative to all of the following four questions, as suggested in the revised diagnostic criteria of the International RLS Study Group (IRLSSG) [15,22].

- Do you ever get an uncomfortable sensation in your lower legs (below the knees), which makes you want to move your legs after sitting still for only a short while?
- Does the sensation go away (even partly) when you move your legs?
- Is the sensation worse at night compared to the daytime?
- Does the sensation only occur when your legs are resting, e.g. lying down or sitting still?

Those subjects who responded in the affirmative to these questions were indeed highly likely to have clinical RLS was confirmed by diagnostic interviews with 20 of the subjects, by a clinician with 10 years experience in the disorder, after completion of the questionnaire.

The questionnaire solicited data in four main areas: demographic data (including current age, frequency of RLS symptoms and age of onset of RLS), RLS-related sleep complaints (specifically difficulty in falling asleep, waking during the night and involuntary movements while awake), any known co-morbid medical disorder and family history of RLS. The Epworth Sleepiness Scale (ESS) [23] was appended to the questionnaire to assess daytime sleepiness.

2.3. Ethical clearance

The study design, including the questionnaire and the radio advertisement were approved by the University of the Witwatersrand Ethics Committee for work on Human Subjects.

2.4. Data analysis

Fisher's Exact Test applied to contingency tables was used for analysis of data. The Mann–Whitney test was used to assess gender differences in current age, duration of symptoms and ESS scores. The relationship between sleep disturbance and duration of symptoms was analysed with a non-parametric analysis of variance (ANOVA).

3. Results

A total of 158 subjects, 95% of whom had Caucasian ancestry, and 63% of whom were women, fulfilled

Table 1
Demographic data for the total population of RLS subjects as well as divided by gender

Feature	Total ($n=158$)	Males ($n=58$)	Females ($n=100$)	P value
Current age (mean±SD)	49±16	50±14	49±17	ns
RLS symptoms>4 days per week (% of patients)	86	85	87	ns
Known family history (% of patients)	63	54	68	ns
Ratio of female to male-affected relatives	2.3	1.6	2.9	ns
ESS score	8.3±5.0	9.0±4.9	7.9±5.1	ns

ESS, Epworth Sleepiness Scale. P value indicates difference between genders using either Mann–Whitney test (age and ESS) or Fisher exact (significance $P<0.05$).

Table 2
Prevalence of individual symptoms and symptom combinations for the total population as well as differences between male and female subjects

Symptoms	Total ($n=155$)	Males ($n=58$)	Females ($n=97$)	P value for gender difference
Involuntary movements while awake	14 (9)	6 (10)	8 (8)	ns
Sleep onset difficulties	5 (3)	3 (5)	2 (2)	ns
Waking during the night	8 (5)	4 (7)	4 (4)	ns
Any two symptoms	59 (38)	26 (45)	33 (34)	ns
All three symptoms	66 (43)	18 (31)	48 (50)	<0.05
None	3 (2)	1 (2)	2 (2)	ns

Significance $P<0.05$. Numbers in brackets indicate percentages.

the criteria for analysis of the questionnaire. Table 1 shows demographic data related to the subjects current age, daytime sleepiness and RLS status: there were no statistically significant gender differences in any of the demographic variables listed. Of all the subjects with RLS, 63% were aware of a positive family history of the condition, but there was no difference in gender. The increased proportion of female-affected relatives compared to male-affected relatives was significant ($P<0.05$) for both female and male subjects.

Table 2 shows an analysis of gender differences in the three sleep-related symptoms included in the questionnaire. More than two-thirds of subjects identified that they suffered from the sleep-related symptoms. However, a minority (17%) complained of a single symptom, 38% had two symptoms and the greatest proportion (43%) had all three symptoms. Though they fulfilled the criteria for diagnosis of RLS, 2% of the patients had none of the three sleep-related symptoms.

There was no statistically significant gender bias in the subjects who presented with isolated symptoms nor in those presenting with any pairs of symptoms. However, among those subjects presenting with all three sleep-related symptoms, there was a significantly increased number of women.

The duration of RLS symptoms for the total population as well as different genders is indicated in Fig. 1. The majority of patients had been aware of symptoms for less than 15 years and there was no significant gender bias. There was no significant relationship between number of symptoms and duration of RLS for the total population or between genders.

Our analysis of co-morbidity in the subjects fulfilling the criteria for RLS showed that a significantly greater proportion of female subjects compared to male subjects had been diagnosed with hypothyroidism; in fact none of our male subjects had hypothyroidism (Fig. 2). There was no gender bias in prevalence for any of the other associated conditions. There was a high incidence of back injury (39%) in both genders and the injury occurred before the onset of RLS in 59% of these subjects. The overall incidence of anxiety (2%) and depression (8%) was low.

4. Discussion

We have investigated, by questionnaire analysis, a cohort of subjects previously recruited from responses to print and radio advertisements with a putative diagnosis of RLS as defined by the International RLS Study Group. Due to the high percentage of women responding, we looked for any gender bias in a variety of presenting features, but for most of the variables we assessed there was no gender bias.

We were able to detect a gender bias in sleep-related symptoms, but it was subtle. No single symptom nor pair of

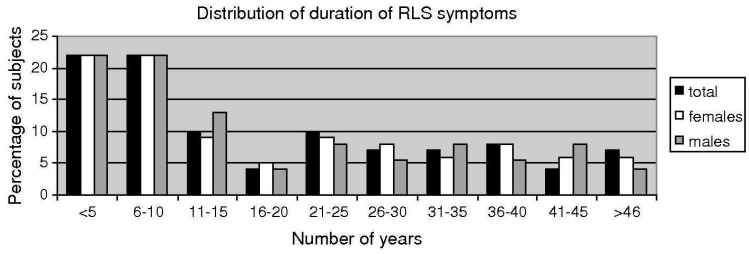


Fig. 1. The distribution of duration of RLS symptoms by gender.

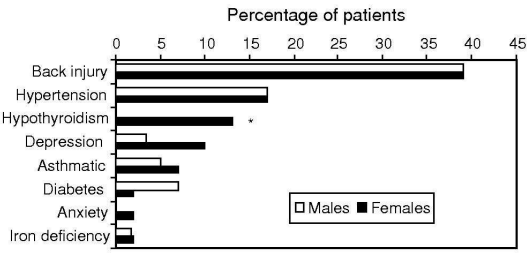


Fig. 2. Gender differences in previously diagnosed associated complaints in subjects presenting with restless legs syndrome. *Significantly different $P<0.05$.

symptoms differed in prevalence between men and women, but a high total proportion and disproportionately more women were likely to present with all three symptoms analysed than were men. These findings were, however, not related to the duration of RLS symptoms. We also identified a disproportionate increase in previously diagnosed hypothyroidism in female subjects, but no gender bias in seven other associated complaints. In addition, both male and female subjects were more aware of female-affected relatives than of male-affected relatives.

The high proportion of subjects with all three sleep-related symptoms may have been the results of the method of sampling, as a higher symptom load would increase the likelihood of response to our advertisements. Other limitations of this study are the disproportionate number of Caucasian patients in an area of the world where Caucasians form a minority of the population at large, the small sample size and the wording of the questions. Both adverts reach a multi-cultural population, but the high Caucasian selection may be due to many factors which could include ethnic differences in the incidence of RLS or differing impacts of RLS on lifestyle. The small sample size may have increased the number of statistical errors and may explain why male subjects did not have significantly fewer symptoms than female subjects. The wording of some of the questions differed from the original International RLS Study Group (IRLSSG) questions in order to reflect local language restraints, and this may have influenced the diagnostic accuracy.

The gender bias in sleep complaints with RLS is similar to the gender bias found in other types of insomnia. This partially confirms our proposal that female subjects with RLS are likely to have more sleep disturbance than male subjects with RLS. Ours is the first study to describe the multiple symptom combinations in this fashion. We did not, however, confirm our suspicion that increasing duration of symptoms played any role in the gender bias observed or even in symptom load.

We also had proposed that any differences in the gender presentation of RLS may have been the result of a gender bias in co-morbid medical disorders. However, with the exception of hypothyroidism, our women subjects with RLS were no more or less likely to have co-morbidities with a gender bias than were our men subjects. It is therefore unlikely that artefacts resulting from co-morbidities contribute to observed gender bias in RLS.

The high incidence of associated back injuries, particularly those occurring before the onset of RLS, raises a potential role for spinal cord injury in the initiation or development of RLS. The relationship of frequent co-morbidities, and particularly back injury, to RLS requires further study.

Our third hypothesis involved the inheritance pattern of RLS. As has been reported in previous studies [9,24], approximately two-thirds of our subjects were aware of a family history of RLS. Ours is the first study, however, to report a female dominance in the affected family members whom the subjects recall. Ongoing genetic studies may explain the basis of this gender dominance. However, the trends we found in reported family history may have been based on better communication about symptoms by female patients to their families or on women being more severely affected by the disorder.

Future studies need to explore the combinations of sleep-related symptoms further, and their relationship to the perceived severity of RLS as well as the possible reasons for the high response among the Caucasian population in South Africa.

In conclusion, we have shown that patients fulfilling a putative diagnosis for RLS and seeking help are more likely to be women and have a higher sleep-related symptom load despite no difference in duration of RLS symptoms. There is also a perceived preponderance of female relatives with RLS in both genders. This data supports our original hypothesis and advances explanation for the increased prevalence of women in RLS treatment studies.

References

[1] Hening W, Allen R, Earley A, et al. The treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999;22: 970–99.

[2] Abetz L, Allen R, Follet A, et al. Evaluating the quality of life of patients with restless legs syndrome. Clin Ther 2004;26(6): 925–35.

[3] Benes H, Heinrich CR, Ueberall MA, Kohnen R. Long-term safety and efficacy of cabergoline for the treatment of idiopathic restless legs syndrome: results from an open-label 6-month clinical trial. Sleep 2004;27(4):674–82.

[4] Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994; 17:739–43.

[5] Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 2000;54:1064–8.

[6] Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic movement disorder in the general population. J Psychosom Res 2002;53:547–54.

[7] Nichols DA, Allen RP, Grauke JH, et al. Restless legs syndrome symptoms in primary care: a prevalence study. Arch Intern Med 2003; 163:2323–9.
[8] Hening W, Walters AS, Allen RP, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms and treatment) primary care study. Sleep Med 2004;5:237–46.
[9] Walters AS, Hickey K, Maltzman J, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology 1996;46:92–5.
[10] Winkelman J, Wetter TC, Collado-Seidel V, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 2000;23:597–602.
[11] Manber R, Armitage R. Sex, steroids and sleep: a review. Sleep 1999; 22:540–55.
[12] Li RH, Wing YK, Ho SC, Fong SY. Gender differences in insomnia—a study in the Hong Kong Chinese population. J Psychosom Res 2002; 53:601–9.
[13] Voderholzer U, Al-Shajlawi A, Weske G, et al. Are there gender differences in objective and subjective sleep measures? A study of insomniacs and healthy controls. Depress Anxiety 2003;17:162–72.
[14] Rosenthal TL, Bryant ES, Lemmi H. Gender differences dominate sleep disorder patients' body problem complaints. Arq Neuropsiquiatr 1994;52:471–5.
[15] Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995;10:634–42.
[16] Vallerand AH, Polomano RC. The relationship of gender to pain. Pain Manag Nurs 2000;1(Suppl. 1):8–15.
[17] Unruh AM. Gender variations in clinical pain experience. Pain 1996; 65:123–67.
[18] Sevim S, Dogu O, Kaleagasi H, et al. Correlation of anxiety and depression symptoms in patients with restless legs syndrome: a population based survey. J Neurol Neurosurg Psychiatry 2004;75: 226–30.
[19] Banno K, Delaire K, Walld R, Kryger MH. Restless legs syndrome in 218 patients: associated disorders. Sleep Med 2000;1:221–9.
[20] Trenkwalder C, Seidel VC, Gasser T, Oertel WH. Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. Mov Disord 1996;11:389–94.
[21] Lazzarini A, Walters AS, Hickey K, et al. Studies of penetrance and anticipation in five autosomal-dominant restless legs syndrome pedigrees. Mov Disord 1999;14:111–6.
[22] Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations and epidemiology. A report for the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101–19.
[23] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–5.
[24] Montplaisir J, Boucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of Restless Legs Syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12: 61–5.

CHAPTER 5

SPONTANEOUS SENSATIONS AND MOTOR EVENTS

By definition, both the sensory disturbance of RLS and the motor events of PLM are spontaneous in nature. Spontaneous activity of the nervous system implies a general increase in the excitability of the neurones in the central nervous system.

Excitability of a neuron refers to the tendency of the neuronal membrane to produce a train of action potentials (Devor 2006). An increased (hyper) excitability of a neuron would imply that the resting membrane potential is relatively depolarised compared to the normal state. If the resting potential is raised but still below the threshold potential for action potential creation, then any sub-threshold stimulus may be able to move the potential to reach threshold and start a train of action potentials producing an exaggerated response to the stimulus. If the resting membrane potential is depolarised above the threshold potential then spontaneous action potentials occur which may then produce spontaneous sensations or motor events.

In an axon an increase in excitability is caused by a change in ionic flux within the neuron allowing more ions (usually sodium) to cross the membrane causing depolarisation of the membrane. The impact of an increase in sodium channel permeability, creating a pacemaker effect in the neuron, has been well documented and is considered to be the likely mechanism in the creation of spontaneous neuropathic pain as well as the mechanism, presumably, for paraesthesias and dysaesthesias (Devor 2006). This increase in sodium flux across neuronal membranes can occur due to changes in general ion concentrations within the body but this is unlikely to be important in the pathogenesis of RLS and PLM. Of more importance to this discussion is a possible

change in the balance of incoming synaptic potentials to the neurones in question in favour of more excitatory potentials or less inhibitory potentials. This may occur due to loss of inhibitory synapses or an increase in excitatory synapses or a combination of both mechanisms either by loss of neurones themselves or else by changes in neurotransmitter concentrations.

Whatever the underlying mechanisms, to create the combined disorder of RLS and PLM, the increased excitability must occur in both the sensory and motor system in a similar fashion to that occurring in spinal injury patients (Finnerup et al 2003; Trenkwalder and Paulus 2004).

5.1 Increased excitability of the sensory system.

As in other sensory research it is in the nociceptive pathways where most research into the phenomena of both exaggerated response to stimuli, in the form of hyperalgesia and allodynia, as well as spontaneous events, in the form of paraesthesias, dysaesthesias and frank pain has been carried out. Given the possible relationship between pain and RLS it may be justified to use these principles in the context of the sensory phenomena associated with the disorder of RLS.

5.1.1 Exaggerated response to stimuli - allodynia and hyperalgesia

If, as occurs in a state of increased excitability, some neurons of the nociceptive pathway are relatively depolarized (sensitized) before the application of a stimulus then a relatively exaggerated response to that stimulus is expected. A response from a usually non-noxious stimulus can be upgraded to the point where the signal is perceived as noxious – termed allodynia. If the intensity of pain from a usually painful stimulus is enhanced so that the stimulus appears to be more painful than in the normal state then the condition is referred to as hyperalgesia (Meyer et al 2006). Most typically both allodynia and hyperalgesia occur when there is central sensitization of the spinal cord in patients with chronic pain or spinal cord injury (Tracey 2005; Suzuki et al 2004; Finnerup et al 2003). Allodynia produced by either tactile, thermal or mechanical stimuli and hyperalgesia produced by either punctuate, mechanical or dynamic stimuli are typical features of many types of both acute and chronic pain (Meyer et al 2006).

Due to a common underlying mechanism allodynia and hyperalgesia are often associated with spontaneous sensations such as paraesthesias, dysaesthesias and frank pain.

5.1.2 Spontaneous activity - paraesthesias, dysaesthesias and pain

Various, slightly different, definitions of these spontaneous sensory events are in use. Paraesthesias can be defined as “spontaneous sensations without external stimuli which are abnormal and frequently unpleasant” (Kandel et al. 2000). The European Federation

of Neurological Societies defines paraesthesias as “abnormal but not unpleasant” when compared to dysaesthesias which are “abnormal and unpleasant” (Cruccu et al. 2004).

Paraesthesias and dysaesthesias are traditionally described in patients with pain due to neurological lesions (neuropathic pain) such as those occurring in peripheral nerves, as in carpal tunnel syndrome (Nora et al. 2005) or more centrally in multiple sclerosis (Beiske et al. 2004), and spinal cord damage (Beric et al. 1988; Finnerup et al. 2003). The presence of these spontaneous sensations in painful conditions is useful to discriminate between neuropathic and nociceptive pain (Boivie 2006). In fact, very rarely are paraesthesias and dysaesthesias considered or measured as independent entities. The origin of paraesthesias and dysaesthesias is presumed to be same as that for pain in neuropathic pain states as a chronic axonal injury leading to changes in Na+ channels resulting in ectopic impulses (Rizzo et al. 1996; Devor 2006; Woolf 2004). Plastic changes may also occur in the neurons of the spinal cord causing central sensitization thus increasing the responsiveness of the sensory system (Johnson 1997).

The unusual modalities of sensations observed in paraesthesias and dysaesthesias may be explained by the unusual origin of the impulses. Sensation types are usually coded by the specificity of peripheral recptors involved in the generation of such impulses. Sensory neurons once in the spinal cord, however, carry multiple modalities of sensation and spontaneous activity in such a group of such diverse neurones may then lack the appropriate coding for modality and intensity usually supplied by the receptors. The information received by the higher centres of the sensory system would then be abnormal

in format and thus abnormal sensations may be perceived. Presumably, the more nociceptive neurons involved in this generalised ectopic activity the more unpleasant the sensation becomes. Research on this topic is lacking possibly due to the lack of a measurement tool both to assess the quality of the sensations described as paraesthesias and dysaesthesias, and to determine the links between these sensations and neuropathic pain.

5.1.3. Measuring sensory events

Measuring sensations has really focussed on those associated with pain, including allodynia and hyperalgesia, as being the most clinically important sensation. Thus various subjective scales have been created ranging from the simple visual analogue scale, or numerical scales or those using words which are primarily designed to measure the intensity of pain only (Melzack and Katz 2006). Measurement of pain threshold and tolerance as well as allodynia and hyperalgesia involves the use of various pain algometers to induce a painful stimulus in order to provide a numerical value to the pain perceived.

The techniques to document the presence of allodynia and hyperalgesia involve the use of experimental stimulation of the nociceptive and/or non-nociceptive pathways such as the application of von Frey hairs (for tactile sensation) or thermodes (for thermal sensations) (Meyer et al 2006). The intensity of the pain induced is compared, using subjective

scales, to other non-affected parts of the body or normal subjects and if higher than expected indicates the presence of allodynia or hyperalgesia.

In the field of spontaneous sensations that are not painful but may occur in painful conditions there are currently no specific measuring scales to assess the nature or descriptive qualities. The presence or absence of paraesthesias and dysaestheias are included in longer scales to measure neuropathic pain such as in the Neuropathic Pain Symptoms Inventory (Bouhassira et al. 2004).

In the search for such a measuring tool for these sensory events, their association with neuropathic pain is most fortunate. There are many tools to measure pain and using such tools to measure these non-painful sensations may be helpful. Measuring only the intensity of pain or using tools that assume pain is present would not be appropriate if pain is absent such as in most cases of RLS. A more useful scale would be one which relied more on qualitative criteria such as the description of sensations used in the McGill Pain Questionnaire (Melzack 1975) (see Appendix 1). The McGill Pain Questionnaire (MPQ) was the first validated questionnaire to recognize the usefulness of the patients' description of painful sensations to define both the type of pain present as well as the severity of the pain. Originally developed from patient descriptions of painful experiences the scale has been used for 30 years with very few modifications apart from a shortened version (Wright et al. 2001). The scale is used for both qualitative as well as quantitative assessment of painful conditions including measuring the reduction in

intensity of pain one would expect to find in response to treatment (Melzack and Katz 2006).

The scale consists of 78 words divided into 20 groups differentiated by perceived type of pain. Subjects choose one or no word from each group. Significance is given to a particular word if more than 30% of respondents agree that the description is valid for that type of pain. This is a relatively low number and may not be high enough; however, the 30% value has been used quite extensively and appears to be acceptable. Different combinations of verbal descriptors have been found to occur in different painful conditions but attempts to differentiate between nociceptive or neuropathic pain have not been very successful. (Dubuisson and Melzack 1976). Despite a lot of work in the field authors disagree on the words that may be diagnostic of neuropathic pain. Some of the suggested words include:

Throbbing, stabbing, sharp, burning (Dubuisson and Melzack 1976),
Shooting, Stabbing, electric shocks (Bouhassira et al. 2004),
Tingling and “pins and needles” (Siddal and McClelland 2006)

It is not clear from the papers attempting to describe neuropathic pain whether the non-painful phenomena associated with neuropathic pain were excluded or included in the choice of descriptive words. If the descriptive characteristics associated with paraesthesias and dysaesthesias were not measured independently from those associated with the underlying pain then the inclusion of these two different types of sensation may

explain the confusion in the neuropathic pain literature. Patients with neuropathic pain plus paraesthesias and dysaesthesias may have a completely different sensory experience compared to those patients who just have pain. There is only one study, in patients with painful and non-painful phantom limb pain, where the MPQ has been used which showed similar words chosen by both groups of subjects (Katz and Melzack 1991). Thus routine measurement of these sensations is not reported. Added to this uncertainty is the well known phenomenon regarding the uniqueness of the individual response to any noxious stimulus possibly due to previous experiences of pain (Melzack 1975; Melzack and Katz 2006). So for an identical peripheral pain stimulus, such as those provided in the experimental situation, differing descriptions of that painful stimulus may be obtained.

As well as purely descriptive data, two severity indices can be calculated from the MPQ either by adding the total number of words chosen or adding the sum of the ranks of each word chosen within each group. These severity indices usually correlate quite well with intensity scores gained from the use of other scales such as the visual analogue scale. Thus, if the MPQ is able to measure paraesthesias and dysaesthesias in a descriptive sense, it may be possible to measure changes in severity of these non-painful phenomena as well.

Apart from the purely subjective assessment of sensation as indicated above, the response of central sites in the nervous system involved in the interpretation of various sensations to sensory stimuli can be measured objectively. Work in this area has focussed on imaging techniques such as the scanning procedures associated with Functional Magnetic

Resonance (fMRI) and Positon Emittance Tomography (PET). During studies on pain there is increased activity of many areas of the brain including the thalamus, many areas of the cortex, basal ganglia, cerebellum, the amygdala and hippocampus (Tracey 2005). The specific areas activated depend on the type of pain and whether the pain experience is chronic or experimental.

Another way to investigate sensations is to look at treatment modalities which are used to reduce the severity of sensations and then use the mechanism of action of such drugs to understand underlying pathogenesis. As mentioned previously, paraesthesias and dysaesthesias are most usually found with neuropathic pain, thus resolution of painful and non-painful sensations with common treatment options may suggest similarities in origin. Effective treatment of neuropathic pain includes the use of the anticonvulsants gabapentin and carbemazepine which act by blocking sodium channels in neurones or induce changes in GABA related pathways (Sindrup and Jensen 1999; Zaremba et al 2006). Anti-depressants such as amitryptiline are demonstrably effective in treating neuropathic pain (Sindrup and Jensen 2001). The impact of all these drugs on the non-painful components of neuropathic pain is unknown.

The lack of adequate measuring tools for non-painful sensations from any source has, I believe, compromised the measurement and understanding of the sensations associated with RLS.

5.1.4 Measurement of the sensory dysfunction of RLS

There has been a distinct lack of formal measurement of the sensations of RLS or comparison of the sensations of RLS to those occurring in other clinical states. Evidence of a hyperexcitable state within the central nervous system may imply a similar origin to those of paraesthesias and dysaesthesias.

The hyperexcitable spinal cord origin of the sensations in RLS is suggested by the induction of RLS in various spinal conditions such as lumbosacral radiculopathy (Walters et al. 1996), degenerative spondylolisthesis (Frymoyer 1994) and transverse myelitis (Brown et al. 2000). Thus the concept of the sensations of RLS being created by ectopic impulses in a hyperexcitable spinal cord may be a valid one (Trenkwalder and Paulus 2004).

Descriptive assessment or any measurement of the sensations of RLS has not been reported. Anecdotal reports from sufferers of RLS describe the sensations as unusual and difficult to describe. Descriptive words such as tingling, tearing, tightening (Wetter and Pollmacher 1997), jittery, creepy crawly, shock-like (Montplaisir et al. 2005) as well as pulling and crawling (Winkelmann et al. 2000) are used. A bulletin from the National Institute of Health gives the following terms to describe RLS: creeping, crawling, itching, burning, searing, tugging, indescribable, pulling, drawing, aching, and pain (Thorpy 2000). Some sufferers prefer to use phrases such as “like an electrical current”, and “like worms or bugs crawling under my skin” to describe these unusual sensations. The

apparently unique sensations described by individual patients may be explained in a similar fashion to that of ectopic impulses from multiple sensory neurones similar to those occurring in neuropathic pain (Bouhassira et al 2004; Woolf 2004; Devor 2006). No prevalence data or relation to severity of RLS for the various words given in the descriptions above has been reported and no research on the underlying mechanisms within the spinal cord, or other areas, such as has been done for neuropathic pain, has been performed in patients with RLS.

The severity of RLS has been measured using three different scales. The first, a visual analogue scale uses similar anchor points to those of pain and can be used quite successfully (Tribl 2005). The second, the John Hopkins severity scale is limited to a single question, the time of day when the sensations are first noticed, but is still valid as a measure of severity (Allen and Earley 2001). The third scale developed by the International Restless Legs Syndrome Study Group (IRLSSG) uses ten questions including many related to the impact of RLS on quality of life to assess severity (Walters et al 2003). None of these assessment tools use the descriptions of the sensations themselves as part of the severity indices and thus are limited in a similar fashion to the simple scales used for measuring pain.

A similarity between the spontaneous sensations usually associated with neuropathic pain and those of RLS has been suggested. The International Restless Legs Syndrome Study Group (IRLSSG) elected at one stage to call the spontaneous sensations associated with RLS paraesthesias or dysaesthesias noting, however, that the sensations of some patients

could not be classified in this manner (Walters 1995). The NIH panel on RLS re-defined the sensations as “unpleasant and uncomfortable” but refrained from calling them paraesthesias and/or dysaesthesias (Allen et al. 2003). The association of “unpleasantness”, being the presence of a negative emotional component to a sensation, is most commonly associated with pain as expressed by the International Association for the Study of Pain (IASP): “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey 1991). However, only 40% of patients with RLS describe their sensations as frankly painful (Winkelmann et al. 2000). However, the conversion of non-painful perceptions to those which are painful occurs fairly regularly in clinical pain settings such as in allodynia (Meyer et al 2006). Thus painful RLS may simply represent an increased severity of the non-painful version of RLS. Another fairly unique quality of the sensory disturbances associated with RLS is the urge to move in order to escape the sensations. This quality is unusual for sensory experiences and has not been described for any other paraesthesias and dysaesthesias, such as associated with neuropathic pain, but forms part of the definition of the sensation of tickle and pain itself (Melzack and Katz 2006; Selden 2004).

A further link to pain has been suggested in a study reporting an abnormality in pain processing in RLS patients with the finding of mechanical hyperalgesia, without tactile allodynia (Stiasny-Kolster et al. 2004). Mechanical hyperalgesia occurs in patients with neuropathic pain but is usually associated with tactile allodynia. The presence of one without the other in patients with RLS indicates a unique type of sensory abnormality but

a sensation that may, nevertheless, have some links to neuropathic pain. Interestingly, the hyperalgesia was found in both the hands and feet while the RLS symptoms were limited to the feet, suggesting a wide ranging change in the state of the spinal cord in these patients (Stiasny-Kolster et al. 2004).

When using treatment modalities to compare sensations, there are many similarities between treatments providing relief from the sensations of RLS and those providing relief from painful conditions. Medications used to treat pain such as codeine (Walters et al. 1993) and the anti-convulsants Gabapentin (Garcia-Borreguero, Larrosa et al. 2002) and carbemazapine (Zucconi, Coccagna et al. 1989) used for neuropathic pain have all been successfully used to reduce the sensory symptoms associated with RLS. Discordant with this theory is the prominent use of antidepressants to treat neuropathic pain, and the conflicting data for the impact of antidepressants on the sensory discomfort associated with RLS (Dorsey et al. 1996; Sindrup and Jensen 1999; Micó et al 2006). Another treatment link to pain, although slightly different is that the use of non-opioid analgesics, presumably for painful conditions, may in fact be a risk factor for development of RLS (Leutgeb and Martus 2002).

The imaging studies of central sensory areas that have been done in subjects with RLS show a similar pattern to those of pain. There are increases in activity on functional MRI within the thalamus during the sensations of RLS and changes in regional blood flow favouring those areas of the caudate and cingulate gyrus usually associated with painful conditions (San Pedro et al. 1998; Bucher et al. 1997).

To determine whether a new sensation, such as that occurring in RLS, fulfils the criteria for paraesthesias, dysaesthesias or even pain, and what type of pain, there needs to be a specific and discriminatory measuring tool. Given the lack of formal assessment of non-painful paraesthesias and dysaesthesias of other origins it is difficult to compare the sensations associated with RLS with these sensations. Despite the lack of data using the word descriptors contained in the MPQ for non-painful sensations the questionnaire has been used successfully in painful RLS (von Spiczak et al 2005). If we consider that the painful and non-painful sensations in RLS may form a continuum, both in clinical symptoms and pathophysiological mechanisms, similar to that in neuropathic pain, there is no reason why the MPQ should not be used to assess the non-painful sensations. Using this questionnaire to describe the sensations associated with RLS and comparing this description to other spontaneous sensations as well as pain may help define the type of sensation experienced in RLS. The similarity of the hyperalgesia to that of neuropathic pain and the presence of painful RLS in a significant minority of RLS patients would suggest that the RLS sensations may originate in the nociceptive pathways thus validating the use of the MPQ to measure such sensations. Additionally, the data could confirm or reject any link to neuropathic pain which could aid in understanding the source and the neurotransmitters involved which may then aid in better pharmaceutical targets for treatment.

In conclusion, the evidence in regards to the sensory discomfort associated with RLS would tend to indicate that there is an increased excitability in the nervous system

creating exaggerated and spontaneous sensations very similar to those of pain. These sensations have, however, not been adequately measured partly due to the lack of a validated measuring instrument. Further, if one accepts that RLS and PLM are one condition, this would imply that the motor phenomena associated with PLM must be explained by the same hyperexcitability as would explain the sensory phenomena of RLS.

5.2 Increased excitability of the motor system.

Hyperexcitability in the neurones of the motor pathways would produce similar events such as those described above in the sensory system with exaggerated responses to stimuli and spontaneous events. In the motor system the exaggerated response to stimuli is seen as hyperreflexia, and spontaneous activity would present as involuntary muscle activity.

5.2.1 Exaggerated response to stimuli - Hyperreflexia

The most common cause of hyperexcitability of the nervous system is in the case of separation of the spinal cord from higher centres of control such as occurs in an upper motor neurone lesion. In such cases a classical tetrad of signs is observed: increased deep tendon and other reflexes (hyperreflexia), release of primitive reflexes such as a Babinski sign, increased muscle tone and spasticity (Kandel et al. 2000; Ditunno et al. 2004). These signs result from an increased excitability of the spinal cord caused both by a loss

of inhibitory impulses as well as synaptic plasticity and thus upregulation in the response of the synapses to neurotransmitters (Ditunno et al 2004). Any given stimulus, such as stretch of the muscle spindles in the quadriceps muscle causes an exaggerated reflex. In the case of the plantar reflex, whereas the normal response to stimulation of the sole is plantar flexion of the toes, in the case of the isolated, or hyperexcitable, spinal cord, the toes dorsiflex instead – producing the primitive reflex known as the Babinski sign.

5.2.2 Spontaneous activity – leg movements

Spontaneous activity within the motor system can originate from various areas. The two areas which have been most well researched are those of the spinal cord and the basal ganglia.

Research in the 1950's and 60's showed that the spinal cord was capable of creating movement plans without higher centre control (as cited in Grillner 1985). The movements so created were rhythmical, repetitive and stereotyped and mimicked locomotion. Since that time these rhythmical movements have been extensively studied and are now called central pattern generators (CPGs) (Grillner 1985). Locomotor CPGs have been found in many animals particularly lower vertebrates but also in rats, cats and putatively in humans as well (Capaday 2002; Dietz 2003). The CPG consists of a local network of neurons within the spinal cord which, when activated, is capable of producing movements similar to those occurring during voluntary locomotion (Grillner 1985). Sensory feedback from the stretch of the proprioceptors in the hip joint can induce

activation of the CPGs and locomotion in an animal with a chronic spinal cord lesion (Kandel et al. 2000). Though not strictly “spontaneous” as they require some sensory stimulus, various relatively complicated motor patterns are self-contained within the lower segments of the spinal cord and could be triggered spontaneously by a general increase in spinal cord excitability.

Involuntary movements are most often associated with lesions of the basal ganglia which comprise a group of nuclei located around the lateral ventricles of the cerebrum. The interactions of these ganglia are involved in control of motor function particularly in the selection and termination of motor programs (Grillner et al 2005). Loss of neurotransmitters or neurones in particular areas can produce involuntary (spontaneous) movements ranging from chorea and tremor to ballism (Obeso et al 2002). The type of movement created depends on the area and neurotransmitter affected.

Less often the brainstem can be involved in the creation of involuntary movements as seen in lesions located in the pontine tegmentum which produce involuntary stepping movements (Lee et al 2005). This is confirmed by the production of stepping movements in animal models during direct electrical stimulation of the mesencephalic locomotor region of the brainstem (Grillner 1985).

Thus an increase in excitability of the neurons in any of these three regions can theoretically produce spontaneous movements in the lower limbs of a similar complexity

to that described in PLM. In order to document and define such spontaneous motor events useful and accurate measurements are required.

5.2.3. Measuring motor events

A detailed analysis of all the techniques available to measure differential activity within the entire motor system is beyond the scope of this review. Many of the techniques used, for example in gait analysis, cannot be used during sleep for purely logistical reasons. I have concentrated, therefore, on those techniques that either have already been used or could possibly still be used in research on periodic limb movements.

Probably the first method of measuring motor events was to watch and describe the movement which, although potentially useful, only provides evidence of the final output of the entire motor event. The actual movement produced is only one part of a complicated sequence initiated by activity in motor centres in the brain and basal ganglia, transmission of a signal through the spinal cord/ brainstem, reception of an electrical event by the muscle which then may or may not result in a movement visible to the naked eye. Thus the activity at various points of this motor pathway particularly within the higher centres and at the level of the muscle should be measured objectively in order to gain more insight into the various components that go to produce the final motor event..

Activity within the initiating motor centres of the cortex and basal ganglia as well as co-ordinating centres such as the cerebellum can be measured using scanning procedures

such as Functional Magnetic Resonance (fMRI) and Positron Emission Tomography (PET). The exact techniques are beyond the scope of this review, but by gaining insight into changes in activity within various motor centres the relative contributions of each particular centre during any particular movement can be assessed. It is, of course, problematic, but not impossible, to employ such techniques during sleep.

While the propagation of an electrical impulse to all the muscle fibres and the shortening of the muscle to change the position of bones and joints are, by necessity, related they are not interchangeable. An electrical signal may be measurable, and indicate a motor sequence, but have too small an amplitude to produce a visible movement. Thus the final output at the level of the muscle can be measured either by the electrical activity in the muscles or the mechanical effects of those same electrical signals on the muscles.

To measure the electrical signal, the most common procedure is to record from electrodes placed either on the surface of the skin overlying the muscle or inserted within the muscle itself, by means of a needle. The electrical tracing thus produced is termed electromyography (EMG). Any number of muscles can be recorded simultaneously and increasing the number of muscles recorded obviously provides more information about the underlying motor sequence. Data from four lower limb muscles as well as 16 limb and trunk muscles simultaneously have been used to construct muscle activation patterns occurring during walking in humans (Houck 2003; Ivanenko et al 2004). Changes of muscle activation patterns within walking occurring between individuals and within the same individual are reported (Winter and Yack 1987) as are computerised pattern

recognition techniques to analyse the power and subtleties of such muscle activity (Pelland 2004). Details such as the size and depth of the motor endplate and positions of various motor units within the muscle body can be estimated using many clustered electrodes on each muscle (Zwarts and Stegeman 2003). Finally, a process to define the underlying neural strategy based on the recording obtained from surface EMG recordings has been suggested (Farina et al 2004). None of these techniques have been used to analyse the muscle activity associated with any involuntary movements caused by clinical conditions such as chorea or ballism.

Such extended EMG recordings have been used to describe common patterns between subjects including five motor patterns which could account for the muscle activity during locomotion (Ivanenko et al 2004; Pelland and McKinley 2004). Analysis of the relationship between muscles has also been studied in patients with spinal cord lesions with electrical induction of stepping movements confirming the presence of neural circuits (CPGs) within the spinal cord (Minassian et al 2004). These studies usually analyse the activations from different muscle groups independently and don't relate the activity in one muscle to the others in terms of sequence or timing. There is no simple way to recognise and compare motor activation patterns such as occur in PLM.

The effect of the electrical signals on the muscle itself can be assessed by monitoring the resultant displacement of joints or bones. The most widely known of these techniques is that of actigraphy where accelerometers are attached to the ankle, or other limbs, to monitor displacement of the limbs (Mathie et al 2004). The analogue signals produced by

the displacements are transformed via algorithms into a digital signal. Various ways of using the accelerometers including varying the site of measuring, using tri-axial accelerometers and placing accelerometers on various axes around a limb can be done in order to obtain a more precise measurement of the movements (Ward et al 2005). Accelerometers have also been used in the analysis of involuntary movements associated with clinical condition such as Parkinson's disease (van Emmerik and Wagener 1996).

Unlike the situation of gait analysis, information regarding the origins of the neural strategy and motor events related to PLMs is at an infancy.

5.1.4 Measurement of motor function in RLS and PLM

The original hypothesis for the origin of spontaneous motor events such as PLM was the presence of hyperexcitability of the nervous system. There is some evidence that PLM are likely to occur when there is isolation and, thus by implication, a state of hyperexcitability of the spinal cord. PLM have been described, on overnight polysomnography, in patients with direct spinal cord lesions, particularly during REM sleep. (Yokota et al. 1991; Lee et al. 1996 ; Dickel et al. 1994). Movements similar to those of PLM were also reported to occur in rats within seven days of experimental spinal cord lesions (Esteves et al. 2004). Leg movements with a periodicity and character very similar to those of PLM have also been observed even when there is a transient isolation of the spinal cord such as occurs in patients undergoing spinal anaesthesia (Watanabe et al. 1987; Watanabe et al. 1990).

The presence of exaggerated reflexes or return of primitive reflexes in subjects with RLS and/or PLM would confirm the hyperexcitable nervous system. The H-reflex (Martinelli et al. 1987) and the flexor reflex (Bara-Jimenez et al. 2000) are indeed exaggerated during wakefulness in patients with RLS and PLM. The first visual observations of PLM indicated a similarity to the primitive Babinski sign but no objective studies using either EMG or accelerometry have been done to confirm or deny the resemblance between the Babinski sign and PLM. (Smith 1985; Smith 1987). The presence of a Babinski sign during sleep is not in itself abnormal (Fujiki et al. 1971), but its spontaneous occurrence, as in PLM, may be induced by increased excitability of the spinal cord. The similarity of PLM to the Babinski sign, with dorsiflexion of the ankle as the most common motor activity in both events, resulted in the recommendation to record the electrical activity of the anterior tibialis muscle and to use the ankle joint as the best site to measure the mechanical effects of the event with accelerometry. These recording sites have persisted as the only sites recorded despite early and repeated reports of multiple muscles being involved in the PLM (Guilleminault et al 1975).

The usual measures reported from the EMG recording of the anterior tibialis muscles on an overnight sleep study are: total number of PLM per hour of sleep (PLM index), number of PLM per sequence, the association of PLM with arousals and the relationship to sleep stages (Zucconi et al. 2006). A PLM index of greater than 5 per hour is considered pathological but the relationship of this index to clinical significance is in doubt (Hornyak et al. 2006). The relationship of the PLM to arousals as the significant

clinical events is not clear with no consistent temporal relationship between the PLM and the arousal and a lack of correlation between the presence of arousals and subjective complaints of disturbed sleep, daytime sleepiness or a feeling of being refreshed on waking (Mendelson 1996; Karadeniz et al 2000). Treatment of the PLM in narcolepsy and obstructive sleep apnea also did not guarantee an improvement in sleep quality (Boivin et al. 1993; Haba-Rubio et al. 2005). Only two studies have shown an impact on sleep quality caused by the presence of PLM (Carrier et al 2005; Aksu et al 2007).

The lack of clinical significance of PLM has led to the relevance of recording PLM in clinical diagnostic studies currently being disputed (Mahowald 2001). This has lead to the need to find alternative means of analysing or recording the EMG. Re-analysis of EMGs using the current recording technique has led to the suggestion of a separate index, the periodicity index (PI) but, while interesting and helpful as another measure of PLM, the relevance of this measurement to clinical symptoms or site of origin of PLM has yet to be shown (Ferri et al 2005). The new index does still suffer from the same problem as the previous technique – that of a single muscle recorded and thus a restricted complexity of muscle activations documented.

Limited studies have been performed using an expanded recording technique over more that one muscle group. Provini et al showed that although dorsiflexion of the ankle was the commonest initiating event other muscle groups in the legs initiated the PLM in more than 39% of cases (Provini et al. 2001). The patterns observed in their patients with PLM were not predictable and varied even within the same patient. In another study using

multiple muscle recordings, just less than 50% of the PLM started with muscles other than toe or ankle flexors (de Weerd et al. 2004). Patients were shown to have personal patterns and there did not appear to be a consistent pattern of leg movements more likely to cause arousals. The same lack of constant activity pattern was also found in a third study using the same selection criteria for the PLM that were analysed (Plazzi et al 2002).There were significant limitations to these studies as only leg movements that conformed to current PLM criteria were used, and a subgroup of the total number of leg movements occurring during the night were analyzed in each case. In both studies activation patterns involving multiple muscle groups were common implying that in order to understand the electrical events underlying PLM, multiple muscle recordings appear to be vital.

The spontaneous movement associated with PLM can also occur during wakefulness. Recruitment patterns of movements occurring in wakefulness (PLMW) again showed a lack of a constant recruitment pattern, here defined as the same order of recruitment in at least 80% of the movements (Trenkwalder, Bucher et al. 1996). Anterior tibialis was the most common initiating muscle in thirteen of the eighteen patients, similar to the data on PLM. Any similarity between the activation patterns during wakefulness (PLMW) and those during sleep (PLMS) has not been analysed.

Thus, the muscle activations associated with PLM whether during wakefulness (PLMW) or sleep (PLMS) are not as stereotyped or as simple as previously thought. Despite the wealth of literature on analysis of EMG patterns related to gait analysis, none of these

techniques, or analyses, have been used to analyse the activity associated with PLM or to assist in finding the source of the movements. Muscle activity patterns must be compard to those occurring during locomotion to confirm or deny any similarity between PLM and the spinal cord CPGs associated with locomotion (Capaday 2002).

The use of accelerometry to measure the movements produced by the electrical events associated with PLM, instead of the more expensive polysomnography, is quite common (Ancoli-Israel 2005). Concurrent use of actigraphs and EMG recordings in subjects with suspected PLM has found good correlations between the displacements and activations in some studies and an underestimation in others (Kazenwadel et al. 1995; Ancoli-Israel et al. 2003). Newer actigraph systems which measure displacement in more than one direction or have more sensitive algorithms may improve this correlation (King et al. 2005). For now, the EMG recordings with surface electrodes, which are more sensitive to muscle activity than actigraphy, are still held to be the gold standard to define PLM.

The use of multiple muscle recordings, with a more advanced analysis, and comparison of patterns to other motor events needs to be done in order to determine the origin and significance of PLM. If the PLM activity is indeed associated with hyperexcitability of the spinal cord then the theory of the activation of the CPGs of locomotion being responsible for PLM appears logical. Using techniques usually reserved for gait analysis and comparing the activation patterns associated with PLM to those occurring during locomotion would assist in confirming this hypothesis. For this purposes a method of

classifying and comparing motor activations during sleep with those occurring during voluntary movements during wakefulness is required.

5.3 Appendix

MCGILL PAIN QUESTIONNAIRE

SUBJECT CODE:_____ Date:_____ Time:_____

PRI: S _____ A _____ E _____ M _____ PRI (TOTAL) _____ PPI _____
(1-10) (11-15) (16) (17-20) (1-20)

1
1. Flickering
2. Quivering
3. Pulsing
4. Throbbing
5. Beating
6. Pounding

2
1. Jumping
2. Flashing
3. Shooting

3
1. Pricking
2. Boring
3. Drilling
4. Stabbing
5. Lancinating

4
1. Sharp
2. Cutting
3. Lacerating

5
1. Pinching
2. Pressing
3. Gnawing
4. Cramping
5. Crushing

6
1. Tugging
2. Pulling
3. Wrenching

7
1. Hot
2. Burning
3. Scalding
4. Searing

8
1. Tingling
2. Itching
3. Smarting
4. Stinging

9
1. Dull
2. Sore
3. Hurting
4. Aching
5. Heavy

10
1. Tender
2. Taut
3. Rasping
4. Splitting

11
1. Tiring
2. Exhausting

12
1. Sickening
2. Suffocating

13
1. Fearful
2. Frightful
3. Terrifying

14
1. Punishing
2. Gruelling
3. Cruel
4. Vicious
5. Killing

15
1. Wretched
2. Blinding

16
1. Annoying
2. Troublesome
3. Miserable
4. Intense
5. Unbearable

17
1. Spreading
2. Radiating
3. Penetrating
4. Piercing

18
1. Tight
2. Numb
3. Drawing
4. Squeezing

19
1. Cool
2. Cold
3. Freezing

20
1. Nagging
2. Nauseating
3. Agonising
4. Dreadful
5. Torturing

Present Pain Intensity (PPI)

What was your previous most painful experience? ……..

.....

People agree that the following 5 words represent pain in increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer the questions below, write the number of the most appropriate word given above in the space provided:

1. Which word describes the worst pain you have ever felt? _____
2. Which word describes the worst toothache you have ever had? _____
3. Which word describes the worst headache you have ever had? _____
4. Which word describes the worst stomach-ache you have ever had?_____
5. Which would best describes your present pain? _____

VAS PAIN RATING

In your experience, how would you rate the pain you are currently feeling.

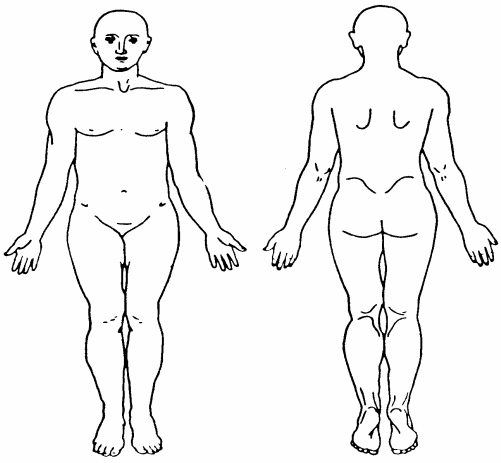
No pain _____ The worst pain I have ever felt

In your life, how much pain have you had from illness and injury.

None _____ As much as anyone could have

LOCATION OF SENSATION

Where is your pain? (Please mark, on the drawings below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal. **ALSO**: if you have one or more areas which can trigger your pain when pressure is applied to them, mark each with an X).



CHAPTER 6

Paper 2: Can the sensory symptoms of restless legs syndrome be assessed using a qualitative pain questionnaire?

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Can the Sensory Symptoms of Restless Legs Syndrome Be Assessed Using a Qualitative Pain Questionnaire?

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Objectives: The sensations of restless legs syndrome (RLS) are described as paresthesias and dysesthesias, sensations which also occur in neuropathic pain. Whether validated pain assessment tools can be used to measure the quality and severity of RLS sensations has not been explored.

Methods: Patients with RLS (n = 25) completed the RLS severity scale of the International Restless Legs Syndrome Study Group, the McGill Pain Questionnaire (MPQ), and a Visual Analog Scale. Words chosen frequently were also compared with those describing different pain types.

Results: The International Restless Legs Syndrome Study Group RLS severity scale score correlated significantly with the Pain Rating Index, and number of words chosen derived from the MPQ, but not with the visual analog scale estimate of pain intensity. The words chosen by patients with RLS showed no significant correlation with words chosen by patients with either neuropathic or nociceptive pain.

Discussion: The quality and severity of the sensation of RLS can be measured on the MPQ, and severity calculated from MPQ indices correlates significantly with a standard RLS severity measure. Thus the nonpainful sensations of RLS appear to be a subclinical form of pain.

Key Words: restless legs syndrome, dysesthesias, paresthesias, McGill Pain Questionnaire

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Restless legs syndrome (RLS) is an neurologic disorder characterized by the presence of uncomfortable sensations in the lower legs, which occur spontaneously urging the sufferer to move their legs.[1] Patients with RLS use words like tingling, tearing, tightening, pulling, and crawling as well as frank pain to describe the sensations that they experience.[2,3] The International Restless Legs Syndrome Study Group (IRLSSG) elected to call the sensations paresthesias or dysesthesias, while cautioning that the sensations of some patients could not be classified in this manner.[4]

The severity of RLS is measured currently by 2 validated questionnaires, the RLS severity scale from the IRLSSG[5] and the John Hopkins severity scale.[6] Neither scale assesses the quality of the RLS sensation itself and there is also no validated instrument to assess paresthesias and dysesthesias from any cause either qualitatively or quantitatively.

Apart from their association with RLS, paresthesias and dysesthesias are associated with neuropathic pain.[7] Up to 80% of patients with RLS report that the sensations are sometimes painful suggesting a similar relationship.[3] Patients with RLS also show some features also seen in neuropathic pain: peripheral neuropathy is present in 36% of late-onset RLS patients[8] and RLS patients have abnormalities in central sensory processing.[9] RLS sensations may also be relieved by treating the patients with analgesic medication to which neuropathic pain responds, such as gabapentin and opiates.[10]

It may be possible, therefore, to describe the sensations associated with RLS with a qualitative scale usually used for painful conditions. The McGill Pain Questionnaire (MPQ) is a semantic instrument used to measure the quality and intensity of pain. The MPQ consists of a list of 78 descriptive words in 20 groups, each group describing a similar type of sensation with differing intensities.[11] Patients are asked to select a word from each group that best describes their sensation. If no word in the group is appropriate the entire group is not selected. Patients with disorders causing neuropathic pain tend to choose different words to describe their pain when compared to patients with disorders producing nociceptive pain.[12,13]

The most commonly used assessment of severity of pain is the Visual Analog Scale (VAS), a 10 cm line anchored at both ends on which the participant places a mark to reflect their current intensity of pain.[14] However, from the MPQ, the ensemble of words chosen can also be used to measure the severity or intensity of the pain. Each word is given a numerical score within its group related to severity and the total sum of these scores constitute a Pain Rating Index (PRI). Another validated approach to assess severity from the MPQ is to count the total number of words chosen (NWC).[11]

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We, therefore, investigated whether the quality and severity of the sensations of RLS could be measured using the MPQ particularly when compared with established measures of RLS severity. We also asked patients to estimate the severity of their sensory symptoms directly on a VAS of pain intensity, and we addressed the question of whether RLS sensations could be compared with either nociceptive or neuropathic pain.

MATERIALS AND METHODS

Patients and Questionnaires

Patients presenting for therapeutic assistance with RLS were asked to participate in the study. Only patients with a confirmed diagnosis of RLS using the National Institutes of Health criteria[1] were enrolled. Patients with secondary RLS, those who had previously taken medication for the treatment of RLS and those with possible confounding medical conditions were excluded from the study. Those eligible patients who volunteered to participate were asked to complete the following questionnaires at interview: a demographic questionnaire defining sex, current age and age of onset of RLS and the IRLSSG RLS severity scale.[5] The IRLSSG severity scale consists of 10 questions which assess the frequency and severity of the RLS sensation plus the impact of RLS on factors such as sleep and mood. The severity score was calculated by adding the numerical responses to all 10 questions.

While experiencing their next RLS sensation (which occurred usually at night within 3 d of interview), patients completed the MPQ and a VAS anchored at "no pain" and "the worst pain I have ever felt." Volunteers were familiarized with the process of answering the MPQ at interview. A Pain Rating Intensity (PRI) was calculated for each participant from the MPQ by adding the scores of words chosen, as described by Melzack and Torgerson.[15] The total NWC by each participant, and the MPQ groups from which words were chosen and the most common individual words chosen were recorded.

Ethics Approval

The project was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand (M03-01-01) and written informed consent was obtained from each participant.

Data Analysis

Scores from the various questionnaires were compared using Spearman nonparametric correlations. Frequencies of words selected by the participants and words from publications describing experiences of pain were analyzed using contingency tables and Fishers exact test. Sex differences were assessed using the Mann-Whitney nonparametric test.

RESULTS

The characteristics of the participants, their RLS history, and their average responses on severity scales are shown in Table 1. There was a known positive family history in 40% of the participants.

All the participants were able to select words from the MPQ, which they believed appropriate to describe their sensory symptoms. Also, all the participants attempted to rate the severity of their RLS on a VAS scale for which the anchor points described pain.

The data displayed in Table 1 also show sex differences. The female participants were significantly older than the male participants but for all other variables there were no significant sex differences and thus all further analyses were performed on pooled data.

There was no significant correlation between the current age, length of time the participant had RLS symptoms or age of onset of RLS, and any of the severity measures, as measured on the RLS severity scale, or the PRI and NWC data from the MPQ (Table 2).

Correlations Between Scales

There was a statistically significant correlation between the IRLSSG RLS severity score and the indices of severity derived from the words chosen from the MPQ (Table 3). There was no significant correlation between the pain scores obtained on the VAS for current RLS pain and any measure of RLS severity or intensity measure from the MPQ.

Analysis of Words Chosen

The median NWC by the participants from the MPQ was 10 with a range of 3 to 17 out of a possible

TABLE 1. Characteristics of the Participants, RLS History and Average Responses on Severity Scales

	Total	Women	Men	Sex Difference *P*
Number	25	19	6	
Age [y, mean (SD)]	47 (18)	52 (17)	33 (8)	0.017
Age of onset of RLS [y, mean (SD)]	28 (15)	31 (14)	18 (14)	0.080
Duration of symptoms [y, mean (SD)]	19 (15)	21 (16)	15 (9)	0.555
MPQ PRI scores [median (CI)]	11 (8,14)	11 (7,15)	11 (7,20)	0.687
NWC [median (CI)]	10 (8,12)	11 (8,13)	8.5 (5,13)	0.555
Pain VAS [n = 22, mm, median (CI)]	18 (11,25)	14 (11,25)	25 (16,64)	0.058
IRLSSG RLS severity [median (CI)]	22 (19,25)	21 (16,28)	25 (19,29)	0.400

Mann-Whitney test for sex differences.
CI indicates confidence interval.

TABLE 2. Spearman Correlation Coefficients (r^2) Between Severity Scales and Current Age, Age of Onset of RLS and Duration of Symptoms

Scale	Current Age	Age of Onset of RLS	Duration of RLS
IRLSSG severity scale	−0.2659	−0.2960	−0.0643
MPQ PRI score	−0.2758	−0.4927	0.1668
VAS current pain	−0.5226	−0.1197	−0.3805
NWC	−0.2146	−0.3599	0.0956

maximum of 20. Groups in which more than 60% of the participants chose a word were: temporal (72%), punctuate pressure (68%), constrictive pressure (84%), dullness (84%), evaluative (100%), and 2 miscellaneous groups, group 17 (72%), and group 20 (80%). The words selected by at least 30% of the participants (%) were: tingling (56), nagging (56), annoying (48), tiring (48), gnawing (40), jumping (40), pricking (36), dull (36), and aching (32).

We compared the frequency of choice, among participants, of individual words with the frequencies found by Wilkie et al[13] in their analysis of words chosen to differentiate nociceptive from neuropathic pain in patients with cancer (Table 4). We confined our analysis to the 4 words chosen most frequently by participants with RLS sensory symptoms and the 4 words chosen most frequently by patients with cancer pain in both nociceptive and neuropathic groups. There was a significant difference between the set of words chosen by participants with RLS, and the sets used frequently by cancer patients to describe both neuropathic and nociceptive pain.

DISCUSSION

We have shown that, irrespective of sex, current age, age of onset of RLS, or the length of time they had experienced RLS, our participants, who had presented for therapeutic assistance with RLS, could select words from the MPQ to describe their sensory symptoms. Nine words from the MPQ were selected by at least 30% of RLS participants. The severity indices of PRI and NWC, on the basis of the words chosen and conventionally used to assess pain intensity, can be calculated for the RLS sensations. These indices calculated from the MPQ for the RLS participants correlated significantly with the measures of RLS intensity obtained from the IRLSSG RLS severity scale. However, neither the conventional measure of RLS severity, nor the indices calculated from the MPQ, correlated with an estimate of pain intensity during RLS measured directly with a VAS. There was a significant difference between the RLS words and both the nociceptive and neuropathic words previously selected by patients with cancer pain.

TABLE 3. Correlations (r^2 Values) Between the Various Severity Instruments

Tests	IRLSSG Severity	McGill PRI (S)	NWC
McGill PRI (by score)	0.5209*	—	—
NWC	0.4391*	0.9376*	—
VAS pain	0.1171	0.1746	0.1202

n = 25, except for VAS scale where n = 22. All Spearman nonparametric correlations.
*Indicates significant correlation $P < 0.05$.

TABLE 4. Comparison Between the Most Common Words Selected by Patients With RLS and the Most Common Words Selected for Nociceptive and Neuropathic Pain in Cancer Patients (Wilkie et al[13])

Words	Lung Cancer Patients n (%)	RLS Participants n (%)
Nociceptive words		
Annoying	132 (39)	12 (48)
Tiring	102 (30)	12 (48)
Aching	90 (26)	8 (32)
Exhausting	87 (25)	5 (20)
Tingling	27 (8)	14 (56)
Nagging	57 (17)	14 (56)
Neuropathic words		
Aching	60 (53)	8 (32)
Annoying	49 (43)	12 (48)
Exhausting	40 (35)	5 (20)
Miserable	37 (33)	3 (12)
Tingling	12 (11)	14 (56)
Nagging	31 (27)	14 (56)

χ^2 for nociceptive = 31.0 ($P < 0.0001$).
χ^2 for neuropathic = 31.5 ($P < 0.0001$).

We conclude, therefore, that the sensory symptoms of RLS share with pain some of the descriptors used in the MPQ, that indices based on the words chosen from the MPQ can be used to estimate the severity of RLS, but that the RLS sensation cannot be assessed accurately on a VAS with pain related anchor points.

Our conclusions are based on the responses of a relatively small number of patients, with a sex bias to females. This sex bias is consistent with the prevalence of RLS.[16,17] Small sample sizes increase the risk of type 2 statistical errors. Although it is unlikely that our conclusions based on lack of correlation with direct measures of pain intensity are invalid, given the very low correlation coefficients for some comparisons (Table 2), bigger samples may reveal sex or other more-subtle differences in the results. However, the small sample size should not confound the strong positive correlations we found, for example, between severity of RLS assessed by the gold-standard IRLSSG criteria and the MPQ PRI.

Given the overlap between the words, which RLS patients use spontaneously to describe RLS and those of the MPQ, it is not surprising that we could calculate a PRI for the RLS participants. The positive correlation between the RLS severity measure and the MPQ would tend to indicate that RLS is in fact a mild pain state. More surprising was the lack of correlation between the PRI obtained in the RLS participants and the VAS assessment, which implies the opposite that in fact the sensations of RLS do not qualify as a pain state. However, dissociation of severity as measured on the

VAS and PRI has been found previously for mild postoperative pain, albeit 24 hours after local anesthetic, with the PRI appearing to be a more sensitive indicator of pain intensity once the VAS drops to low values similar to those found in our patients with RLS.[18]

So whether disassociation between VAS and other intensity scores is the consequence of RLS sensations not qualifying as pain, or the consequence of a lack of correlation of intensity indices in mild pain, requires further research. The lack of correlation should not preclude the possibility of the MPQ being used to describe the quality of the RLS sensation and other paresthesias or dysesthesias.

Comparing data regarding the quality of the sensation from RLS patients and pain experienced by lung cancer patients may appear unusual. The study by Wilkie et al[13] is unique, in our view, in that it attempted to distinguish between words used to describe neuropathic and nociceptive pain, with the pain diagnosed on criteria other than the words themselves, and reported the frequencies for all words selected from the MPQ. Other studies tend to report only the most common words for a particular painful condition, which makes comparison with novel conditions difficult.

The lack of correlation between the sensations of RLS and those of particularly neuropathic pain as experienced by cancer patients suggests a unique character to the RLS sensations. However, these data may reflect on the uniqueness of all paresthesias and dysesthesias as no work has been done on the character of these sensations in the absence of concomitant neuropathic pain. We have shown that in the absence of any other validated scale to measure the quality and quantity of somatosensory events, which are not painful, the use of the MPQ may be profitable.

On the basis of our data, the lack of correlation between the MPQ severity measures and the VAS may be useful in differentiating nonpainful, but still unpleasant, sensations such as paresthesias and dysesthesias from frank neuropathic pain. Characterizing neuropathic pain without excluding the possible unique character of the paresthesia and dysesthesia associated with the pain may help explain the differences obtained previously in various causes of neuropathic pain.[12,19,20] Differentiating and characterizing these sensations distinct from neuropathic pain is necessary to compare them with the dysesthesias of RLS.

Our result, however, do indicate that the sensations of RLS may be similar to that of pain. An association between the sensations of RLS and pain states has been suggested previously. Blood flow to the cingulate gyrus, an area of cortex implicated in pain perception, increases in patients with painful RLS.[21] Patients with RLS also show abnormalities of pain processing in that they exhibit mechanical hyperalgesia without dynamic allodynia.[22] In RLS treatment studies, anticonvulsants such as gabapentin, used as first line analgesia to treat neuropathic pain,[23] have been found to be efficacious in treating RLS.[24] Postamputation phantom RLS, equivalent to phantom limb pain, has been reported[25] and restless hands in patients with carpal tunnel syndrome.[26] To more precisely define the dysesthesias of RLS as neuropathic, more specific neuropathic pain symptom questionnaires[27] need to be used in patients with RLS, although many of the questions may not be valid owing to the nonpainful character of the RLS sensations.

In conclusion, we have shown that both the quality and intensity of the sensory symptoms of RLS can be measured with the MPQ, a validated pain symptom questionnaire. This would imply that the sensations of RLS, which are usually nonpainful, are in fact a form of mild pain probably involving the neurologic pathways usually dedicated to the sensation of pain. Whether RLS sensations can be characterized as similar to those of neuropathic pain requires further study.

REFERENCES

1. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med.* 2003; 4:101–119.
2. Wetter TC, Pollmacher T. Restless legs and periodic leg movements in sleep syndromes. *J Neurol.* 1997;244:S37–S45.
3. Winkelmann J, Wetter TC, Collado-Seidel V, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep.* 2000;23: 597–602.
4. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord.* 1995;10:634–642.
5. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4:121–132.
6. Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. *Sleep Med.* 2001;2:239–242.
7. Woolf C. Dissecting out mechanisms responsible for neuropathic pain: implications for diagnosis and therapy. *Life Sci.* 2004; 74:2605–2610.
8. Polydefkis M, Allen RP, Hauer P, et al. Subclinical sensory neuropathy in late-onset restless legs syndrome. *Neurology.* 2000; 55:1115–1121.
9. Schattschneider J, Bode A, Wasner G, et al. Idiopathic restless legs syndrome: abnormalities in central somatosensory processing. *J Neurol.* 2004;251:977–982.
10. Hening W, Allen R, Earley C, et al. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. *Sleep.* 1999;22:970–999.
11. Melzack R. The McGill pain questionnaire. *Pain.* 1975;1: 277–299.
12. Dubuisson D, Melzack R. Classification of clinical pain descriptors by multiple group discriminant analysis. *Exp Neurol.* 1976; 51:480–487.
13. Wilkie D, Huang H, Reilly N, et al. Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality decriptors. *J Pain Symptom Manage.* 2001;22:899–910.
14. Melzack R, Katz J. *Pain measurement in persons in pain.* In: *Textbook of Pain.* McMahon SB, Koltzenburg M, ed. Elsevier: Philadelphia; 2006:337–351.
15. Melzack R, Torgerson W. On the language of pain. *Anesthesiology.* 1971;34:50–59.
16. Barriere G, Cazalets J, Bioulac B, et al. The restless legs syndrome. *Prog Neurobiol.* 2005;77:139–165.
17. Bentley A, Rosman K, Mitchell D. Gender differences in the presentation of subjects with restless legs syndrome. *Sleep Med.* 2006;7:37–41.
18. Katz J, Clairoux M, Kavanagh B, et al. Pre-emptive lumbar anaesthesia reduces postoperative pain and patient-controlled

morphine consumption after lower abdominal surgery. *Pain*. 1994; 59:395–403.
19. Dudgeon B, Ehde D, Cardenas D, et al. Describing pain with physical disability: narrative interviews and the McGill Pain Questionnaire. *Arch Phys Med Rehabil* 2005;86:109–115.
20. Masson E, Hunt L, Gem J, et al. A novel approach to the diagnosis and assessment of symptomatic diabetic neuropathy. *Pain*. 1989;38: 25–28.
21. San Pedro EC, Mountz JM, Mountz JD, et al. Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus, and anterior cingulate gyrus. *J Rheumatol*. 1998;25:2270–2275.
22. Stiasny-Kolster K, Magerl W, Oertel WH, et al. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. *Brain*. 2004;127:773–782.
23. Levendoglu F, Ogun C, Ozerbil O, et al. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine*. 2004;29:743–751.
24. Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology*. 2002;59:1573–1579.
25. Hanna PA, Kumar S, Walters AS. Restless legs symptoms in a patient with above knee amputations: a case of phantom restless legs. *Clin Neuropharmacol*. 2004;27:87–89.
26. Nora D, Becker J, Ehlers J, et al. What symptoms are truly caused by median nerve compression in carpal tunnel syndrome? *Clin Neurophysiol*. 2005;116:275–283.
27. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptoms Inventory. *Pain*. 2004;108:248–257.

CHAPTER 7

Paper 3: Classifying the sequence and latencies of electromyographic activations of multiple leg muscles reveals subtle differences in motor outputs between sleep stages.

Submitted to Sleep

Classifying the sequence and latencies of electromyographic activations of multiple leg muscles reveals subtle differences in motor outputs between sleep stages.

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Running title: Motor patterns during sleep.

Keywords: Restless legs syndrome, periodic limb movements, electromyograms, sleep stages, motor patterns.

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Abstract

In order to gain more information about periodic limb movements (PLM) a classification which will allow comparison of motor patterns using a recording multiple muscle groups is required. Comparisons can then made across sleep stages and between motor patterns during sleep and motor patterns from known sources, such as gait, in order to find the source of the movements.

Ten patients with restless legs syndrome underwent overnight polysomnograms including surface EMG recordings of the anterior tibialis, gastrocnemius, quadriceps and hamstring muscle groups of both legs. All EMG activations occurring during sleep without regard for current PLM criteria were analyzed and classified according to the order and duration between muscle activations.

A total of 2100 leg movements were analyzed into 80 patterns. A classification system is suggested which defines patterns based on order of muscle activation, accounting for concurrent and sequential muscle activation, as well as total inter-activation duration. All muscle groups were involved in initiation of activations but patterns initiated by anterior tibialis were most common. Results indicate differences between sleep stages in total number of patterns, assemblies and number of unique assemblies. The inter-activation duration is not affected by anatomical placement of electrodes, and duration between initiating activations could not be predicted by complexity of pattern or sleep stage.

The classification system is simple, self explanatory and adaptable. Initial applications suggest reduced excitability of the motor system during slow wave sleep and REM sleep when compared to stage 2 sleep in patients with PLM.

Introduction

Routine measurement of involuntary leg movements, or, more properly muscle activations by electromyograms (EMGs), during sleep has been part of the clinical overnight polysomnogram since nocturnal myoclonus first was described as a disorder in 1953 [1]. Pathological muscle activations, periodic limb movements (PLM), are distinguished from non-pathological activations by standard criteria first described in 1980, revised once in 1993 and again most recently in 2006 [2, 3,4]. These criteria define the minimum amplitude, duration, inter-activation interval, frequency and number of activations which constitute PLM.

All previous research has focused only on the activations which fulfill these criteria despite the lack of correlation with clinical symptoms, time of arousals or sleep disruption [5-8]. One of the reasons for this disparity may be the recording technique which, despite visual evidence that PLM involve multiple muscle groups, has been restricted to a single muscle – tibialis anterior [9]. Previous studies using multiple muscle recordings have shown different patterns in individual subjects but the lack of a single system to describe the patterns generated and the restriction of motor events to those conforming to PLM criteria limit the usefulness of such studies [10, 11]. There is also no way of comparing the motor patterns described in these studies with those from other movements such as those occurring during normal gait. Variations in the patterns of motor events between sleep stages or analysis of the time intervals between activations were not described.

Research using the standard PLM criteria show a reduction in the number of movements from stage 2 to slow wave sleep, and a shortened activation duration and longer inter-activation intervals during REM sleep when compared to NREM sleep implying a gradual reduction in excitability at the neurological source of the movements [12, 13]. Research on the impact of sleep stage on the excitability of the motor system is usually confined to the dramatic inhibition of the motor system during REM sleep [14]. Very little information is available on changes in excitability of the motor system during NREM sleep, though there is slight hyperpolarisation of motor neurons in the transition between wakefulness and NREM sleep [14].

We aimed to record leg movements using surface EMG recordings of multiple muscle groups during sleep and then to use these recordings to construct a useful classification to assist in answering some of these questions. Specifically we were interested in whether use of such a classification, particularly the information on activation sequences and inter-activation durations, could provide new insights into the state of excitability of the motor system during different sleep stages.

Methods.

Subjects

Subjects were recruited from patients, who had never been previously treated for Restless Legs Syndrome (RLS), who now presented for treatment. The RLS was diagnosed on

clinical interview by an experienced clinician (AB) according to the criteria of the National Institute of Health [15]. Patients volunteered for an overnight polysomnogram in the Wits Dial-a-Bed Sleep Laboratory. Bed time was that typical for each patient at home, and the patients were allowed to wake naturally. Standard recording electrodes for polysomnography were attached to measure electroencephalogram (EEG), left and right electro-oculograms (EOG) and submental electromyogram (EMG) activity. Standard pulse oximetry, respiratory recordings using thermistors at the external nares and respiratory effort traces were recorded on any subjects with a history of snoring and subjects with obstructive sleep apnea were excluded from EMG analysis. Polysomnogram and EMG data were stored digitally (EasyEEG2, Cadwell, Kenniwick, Washington. USA). Sleep stages were scored according to Rechtschaffen and Kales criteria[16].

Electromyography

The EMG activity in the legs was recorded using differential surface EMG electrodes. Two gold-plated, 5mm diameter electrodes were applied 30 mm apart on the skin surface over the centre of the belly of each of the Quadriceps, Hamstrings, Gastrocnemius and Anterior tibialis muscles of both legs. EMG activations were included in the analysis if they fulfilled the following criteria: they occurred during sleep, the EMG signal-to-noise ratio was at least two to one, and the activation could be recognized as a discrete event and the time interval between activations of differing muscle groups within the events was ≤4 s. In order to simplify the pattern recognition, reactivation of a muscle group within this time period was taken to signal a new event. All EMG activations, without

regard for standard PLM criteria, were included if they complied with the above criteria. Data from each leg was analyzed independently.

Each set of muscle activations fulfilling the above criteria was termed an EMG "assembly". The specific order and timing of muscle groups within each assembly, were documented by constructing a graphical template on a transparent sheet placed over the computer screen. We then assigned a descriptive label to each assembly (see Fig 1 and 2). The initial letter of the muscle group (**A**nterior tibialis, **G**astrocnemius, **Q**uadriceps and **H**amstrings) identified that a particular muscle group had been activated within the assembly. If the activation of different muscle groups occurred less than 50 ms apart, we separated the identifying letters by a comma, and used the default sequence of letters A, G, Q, H. In effect, we considered such activations as simultaneous. If the activations occurred 50 ms or more apart, we separated the letters by dashes, and ordered the letters according to the sequence in which the muscle groups in that leg were activated. The total inter-activation duration of the assembly (ms) as measured from the beginning of the first activation to the beginning of the last activation in the assembly, was appended to the letter sequence if any intervals between activations within the sequence were $\geq$ 50 ms.

After we had assigned a sequence label to each assembly, we could analyze how many assemblies we detected in each patient and the number of muscle groups activated in each assembly. We identified assemblies which had exactly the same activation sequence of muscle groups, without regard to the interval duration, as having the same "pattern".

We then used the data from eight subjects who had complete data sets and assemblies in all sleep stages for further analysis. We could then analyse the relationship between assemblies and patterns and the inter-activation durations of the patterns. We then applied our classifications to describe how the assemblies and patterns differed, either in number or complexity, between stage 2 sleep, slow wave sleep (comprising stages 3 and 4) and REM sleep. We also assessed whether the interval duration of patterns was influenced by the anatomical arrangement of activated muscle groups or sleep stages.

Ethics approval.

The procedures were approved by the Committee for Research on Human Subjects of the University of the Witwatersrand (M00/04/05).

Statistical analysis

Binomial distribution tables were used to assess right versus left leg differences in number of assemblies and patterns. All data (apart from where otherwise indicated) was analysed for each subject before comparison were made. Results are expressed as median (CI) throughout. Spearman correlations were used throughout for all comparisons. ANOVA plus Dunn's post-hoc test was used to compare patterns occurring during different stages of sleep. Mann-Whitney non-parametric test was used to compare inter-activation durations.

Results:

Classification of patterns of muscle activation.

The age and gender of the subjects, their total sleep time on the recording night, the total number of assemblies and the total number of patterns for each subject are shown in Table 1. Subjects varied widely in the total sleep time, total number of assemblies as well as total number of patterns. Total sleep time was short for most subjects as is typical for subjects with RLS and PLMs [17, 18]. To create the classification we pooled all data and analyzed a total of 2100 assemblies. For technical reasons the assemblies from only the right leg of one subject could be used for analysis. Two subjects had significantly more assemblies on the right leg than on the left leg, and one subject had more assemblies on the left leg but no subject had significantly more patterns on one leg than on the other leg. The total number of patterns observed for each patient was smaller than the sum of those from the right leg and the left leg, implying that there were common patterns obtained from both legs. The total number of patterns, which differed in number of muscle groups activated or order of muscle activation, in pooled data from all the subjects, was 80.

We then used the data from eight subjects as described previously. There was no correlation between the total number of assemblies and the total number of patterns in the subjects (Spearman p=0.083). Of the total assemblies, 42% (21,63) involved the activation of only one muscle group. Although this percentage was higher than those

involving activation of two (19 (10,30)), three (15 (5,44)) and four (14 (6,35)) muscle groups the difference was not significant.

All four muscle groups were involved in pattern initiation: 77% (39,83) of the assemblies started with activation of Anterior Tibialis which was significantly higher than those starting with either Gastrocnemius 4.5% (0,25), Quadriceps 1.8% (0.2,18) or the Hamstrings muscle group (9% (2.5,23). The number of assemblies which involved simultaneous activation of two, three or four muscles as initiating muscles was 7.5% (3.6,23). There was a significant correlation between the total number of patterns and those patterns initiated by anterior tibialis (Spearman p=0.015) but not with any other muscle group. Individual patients frequently showed stereotypical patterns for order of muscles activated. All eight subjects had patterns started by all muscle groups, however, only two patterns were common to all subjects – those of anterior tibialis alone (a) and activation of anterior tibialis followed by activation of hamstrings (a-h).

Duration

An total inter-activation duration of between 0 and 500ms was found to be most common and significantly more assemblies lasted less than 500 ms than longer than 501 ms (p = 0.0046, Mann Whitney. The inter-activation duration, in ms, of patterns (median (CI)) with activation of two muscle groups (200 (100;400)) was significantly shorter than those with three muscle groups activated (850 (450;1200)) but not shorter when compared to patterns with activation of four muscle groups (362 (200;1000)).

In order to assess whether the anatomical arrangement of electrodes was a primary determinant in the inter-activation duration, we compared the only common pattern in all subject (a-h) to the next most common pattern in each subject involving two muscle groups. The only significant difference was in one subject where the pattern of gastrocnemius followed by anterior tibialis (g-a) was significantly shorter than the pattern a-h in the same subject ($p=<0.001$ Dunn's post-hoc test). No other combination was significantly different.

Applications

Patterns and sleep stages

There were significantly fewer assemblies during slow wave sleep ($p<0.05$) and REM sleep ($p<0.001$) when compared to stage 2 sleep (ANOVA with Dunn's post-hoc test) (Table 2). The number of patterns in stage 2 sleep is also significantly higher than in slow wave sleep ($p<0.01$) and REM sleep ($P<0.05$) (ANOVA with Dunn's post-hoc test). There was a significant correlation in REM sleep ($p = 0.0498$ Spearman) between the number of assemblies and patterns but not for stage 2 or slow wave sleep. There were some patterns which were common to all sleep stages but the number of these patterns (3.5 (1,6)) was not significantly different from the number of unique patterns in any particular sleep stage. There was a significant correlation between the number of

assemblies and the number of unique patterns in stage 2 sleep (p=0.015 Spearmans) but not in slow wave sleep (p=0.115) or REM sleep (p=0.069).

In order to assess changes in inter-activation duration of pattern with change in sleep stage two patterns were selected which occurred in all three sleep stages in sufficient numbers to achieve some significance (at least eight data points for each stage). The only two patterns to produce such data both involved only two muscle groups in two different patients (a-h in one subject and g-a in another subject). There was no significant difference in the medians and confidence intervals of the inter-activation durations of the patterns for either pattern in either subject between any of the three sleep stages.

Discussion

We have proposed a classification system for EMG activations recorded from leg muscles during sleep based on the analysis of 2100 assemblies of muscle activation recorded by surface EMG from four muscle groups in each leg, during sleep. Our classification is based on the number of muscle groups activated, the order of activation and the interval between muscle activations. We believe that our classification is simple to apply and self-explanatory, and that being able to label EMG activations in such a way improves our ability to explore the neurophysiological basis of such muscle activations. The 2100 activation assemblies we recorded resolved into 80 distinctive patterns.

All four muscle groups from which we recorded, namely Anterior tibialis, Gastrocnemius, Quadriceps and Hamstrings, initiated patterns in our 10 patients irrespective of how many other groups were activated. There were significantly more patterns initiated by anterior tibialis than by any other muscle group and the two patterns common to all subjects both were initiated by anterior tibialis. Patterns of short (<500 ms) duration were the most frequent. The inter-activation duration of patterns was also not influenced by anatomical placement of electrodes – either between subjects for the same pattern or within subjects for differing patterns.

Muscle patterns differed between sleep stages with more assemblies and patterns occurring in stage 2 sleep when compared to both slow wave sleep and REM sleep. We also obtained data in two subjects which showed that the inter-activation duration of patterns was not determined by the sleep stage. Thus, the classification system allows for quantification of type, complexity and duration of muscle sequence activation, so providing a greatly enhanced tool for analysis of leg muscle activations during sleep.

Whilst many different patterns of activations were observed in our patients it is unlikely that all possible muscle patterns occurred in our limited sample of 10 patients. Other patterns may be found in other groups of subjects; our classification will allow new patterns to be described in a consistent, self-explanatory way. We also did not cover all muscles groups in the legs and extensor digitorum brevis may need to be added for completeness [11]; our classification allows ready incorporation of other groups. We chose an arbitrary time interval (50 ms) to distinguish between virtually simultaneous and

delayed activation of muscle groups. We also set an arbitrary cutoff for maximum inter-activation duration of pattern (4 s), a decision which was subsequently supported by the distribution of activations measured. Future studies may refine those criteria, or may reveal that there is no benefit in distinguishing inter-activation duration. We also did not use any other criteria associated with the definition of Periodic Limb Movements as defined by the World Association of Sleep Medicine criteria [2]. This decision was based on our wish to widen the scope of the recordings to document all possible patterns as well as concern regarding the arbitrary nature of some of the criteria. Critical review of the present criteria, particularly for amplitude, has been suggested recently to gain more sensitivity in the investigation of the periodicity of PLM [19].

Our choice of subjects, being patients with restless legs syndrome, may be justified in order to increase the number of leg movements recorded during sleep and hence the sample size. Whether the data obtained here can be extrapolated to other causes of PLM or not is unclear. The current theory for the generation of PLM, being a hyperexcitable spinal cord may simply be an exaggeration of the normal increase in the excitability of the spinal cord observed during normal sleep, indicated by the presence of Babinski reflexes [20-22]. This may explain the presence of PLM in multiple disorders with differing etiology as well as the presence of PLM in otherwise normal individuals [23-25].

We were surprised by the number of different patterns obtained in our patients, but this has been implied in previous studies suggesting multiple sites of origin for these events even in individual subjects [10,11]. Another option is that some of the activations involving

only 1, 2 or 3 muscle groups may be partial activation patterns of more complex activations involving four muscle groups. Our inter-activation duration data does not, however, support this proposal. Using our classification on more subjects would assist in clarifying this dilemma. We were also pleased to observe that the interval duration of the patterns was not determined by anatomical position of the electrodes. Thus the patterns obtained probably represented a true motor activation pattern generated from an as yet unidentified site, or sites, in the nervous system.

Ours is the first study to look at the impact of sleep stages on the detail regarding the leg muscle activation patterns in subjects with PLM. There were significantly more assemblies, patterns and unique patterns in stage 2 sleep when compared to slow wave sleep and REM suggesting a higher level of motor excitability in stage 2 sleep. There was no difference between the number of assemblies, patterns or unique patterns between slow wave sleep and REM sleep indicating a similar level of motor excitability. Our sleep stage data is thus different to the data obtained in previous studies on PLM during different sleep stages which indicated a difference between slow wave sleep and REM sleep in the character of PLM [12,13]. However, the previous studies only looked at movements which conformed to PLM criteria while we used all movements. Any decrease in excitability between sleep stages is not confirmed by the inter-activation duration data which shows no lengthening of the patterns during slow wave sleep and REM, but the low numbers may have accounted for this effect. The inhibition during slow wave sleep is unexpected given the significant motor inhibition during REM and the apparent lack of such inhibition during slow wave sleep[14]. Thus another mechanism must

be present to account for the reduced muscle activations during slow wave sleep which may have to do with a reduction in level of arousal. The changes seen in motor function during slow wave sleep in our study may be unique to patients with PLM related to RLS. The sleep stage changes in motor activity in patients with PLM related to other disorders may show differing results. The number of unique patterns in each sleep stage and the limited number of patterns common to all sleep stages may confirm that multiple neurological sites are responsible for leg muscle activations during sleep. Future studies, using the classification need to look, in more detail, at whether the complexities of patterns differs between the different sleep stages.

Our classification is considerably simpler than pattern and activity recognition procedures in the field of gait analysis. While various techniques used in movement studies to analyse patterns of motor output cannot be used during sleep for logistical reasons, most only use the different muscle groups in isolation or depend on complicated computer software to determine activity patterns [26,27]. There is no classification similar to ours in the field of gait analysis which could be modified to be used in PLM and still give us results comparable to the ones we obtained. However, using our classification to compare the patterns obtained during gait to those occurring during PLM would help in defining the influence of the spinal central generators as the potential source of PLM motor patterns.

In conclusion, we have proposed a classification system to define EMG excitation patterns occurring in the legs during sleep, which we have used to investigate the state of

the motor system during sleep and which could assist in improving information regarding the state of the motor system during different sleep stages, the neural origin and impact of leg EMG bursts in periodic limb movements and allow comparisons between leg movements occurring in different sleep disorders.

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References:

1. Symonds CP. Nocturnal myoclonus. J Neurol Neurosurg Psychiatry 1953;16: 166-171.

2. Coleman R, Pollack C, Weitzman E. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. Ann Neurol 1980;8:416-421.

3. The ASDA Atlas Task Force. Recording and scoring Leg Movements. Sleep 1993;16: 749-759.

4. Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Med 2006;7: 175-183.

5. Mendelson WB. Are periodic leg movements associated with clinical sleep disturbance? Sleep 1996;19: 219-223.

6. Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Med 2000;1: 163-167.

7. Nicolas A, Lesperance P, Montplaisir J. Is excessive daytime sleepiness with periodic leg movements during sleep a specific diagnostic category? Eur Neurol 1998;40: 22-26.

8. Karadeniz D, Ondze B, Besset A, Billiard M. Are periodic leg movements during sleep (PLMS) responsible for sleep disruption in insomnia patients? Eur J Neurol 2000;7: 331-336.

9. Coleman RM. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. Sleeping and Waking Disorders. Menlo Park: Addison-Wesley, 1982: 265-295.

10. Provini F, Vetrugno R, Meletti S, et al. Motor pattern of periodic limb movements during sleep. Neurology 2001;57: 300-304.

11. de Weerd AW, Rijsman RM, Brinkley A. Activity patterns of leg muscles in periodic limb movement disorder. J Neurol Neurosurg Psychiatry 2004;75: 317-319.

12. Pollmacher T, Schulz H. Periodic leg movements (PLM): their relationship to sleep stages. Sleep 1993;16: 572-577.

13. Nicolas A, Michaud M, Lavigne G, Montplaisir J. The influence of sex, age and sleep/wake state on characteristics of periodic leg movements in restless legs syndrome patients. Clin Neurophysiol 1999;110: 1168-1174.

14. Chase M, Morales F. Control of motoneurons during sleep. In: Kryger MH, Roth T, Dement W, eds. Principals and Practice of Sleep Medicine. Philadelphia, 2005.

15. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4: 101-119.

16. Rechtschaffen A, Kales A. A manual of standardised terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service / Brain Research Institute, 1968.

17. Montplaisir J, Allen R, Walters A, Ferini-Strambi L. Restless Legs Syndrome and Periodic Limb Movements during sleep. In: Kryger M, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. 4th ed. Philadelphia: Elsevier, 2005: 839-852.

18. Bjorvatn B, Leissner L, Ulfberg J, et al. Prevalence, severity and risk factors of restless legs syndrome in the general population in two Scandinavian countries. Sleep Med 2005;6: 307-312.

19. Gschliesser V, Brandauer E, Ulmer H, Poewe W, Hogl B. Periodic limb movement counting in polysomnography: Effects of amplitude. Sleep Med 2006;7: 249-254.

20. 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;115: 1975-1988.

21. Barriere G, Cazalets J, Bioulac B, Tison F, Ghorayeb I. The restless legs syndrome. Prog Neurobiol 2005;77: 139-165.

22. Fujiki A, Shimizu A, Yamada Y, Yamamoto J, Kaneko Z. The Babinski reflex during sleep and wakefulness. Electroencephalogr Clin Neurophysiol 1971;31: 610-613.

23. Dickel MJ, Mosko SS. Morbidity cut-offs for sleep apnea and periodic leg movements in predicting subjective complaints in seniors. Sleep 1990;13: 155-166.

24. Montplaisir J, Godbout R, Poirier G, Bedard MA. Restless legs syndrome and periodic movements in sleep: physiopathology and treatment with L-dopa. Clin Neuropharmacol 1986;9: 456-463.

25. Warnes H, Dinner D, Kotagal P, Burgess R. Periodic limb movements and sleep apnoea. J Sleep Res 1993;2: 38-44.

26. Ivanenko, Y., Poppele, R. and Lacquaniti, F. Five basic muscle activation patterns account for muscle activity during human locomotion. J Physiol 2004;556: 267-82.

27. Pelland L and McKinley P. A pattern recognition technique to characterise the differential modulation of co-activating muscles at the performer/environmental interface. J Electromyogr Kinesiol 2004;14: 539-54.

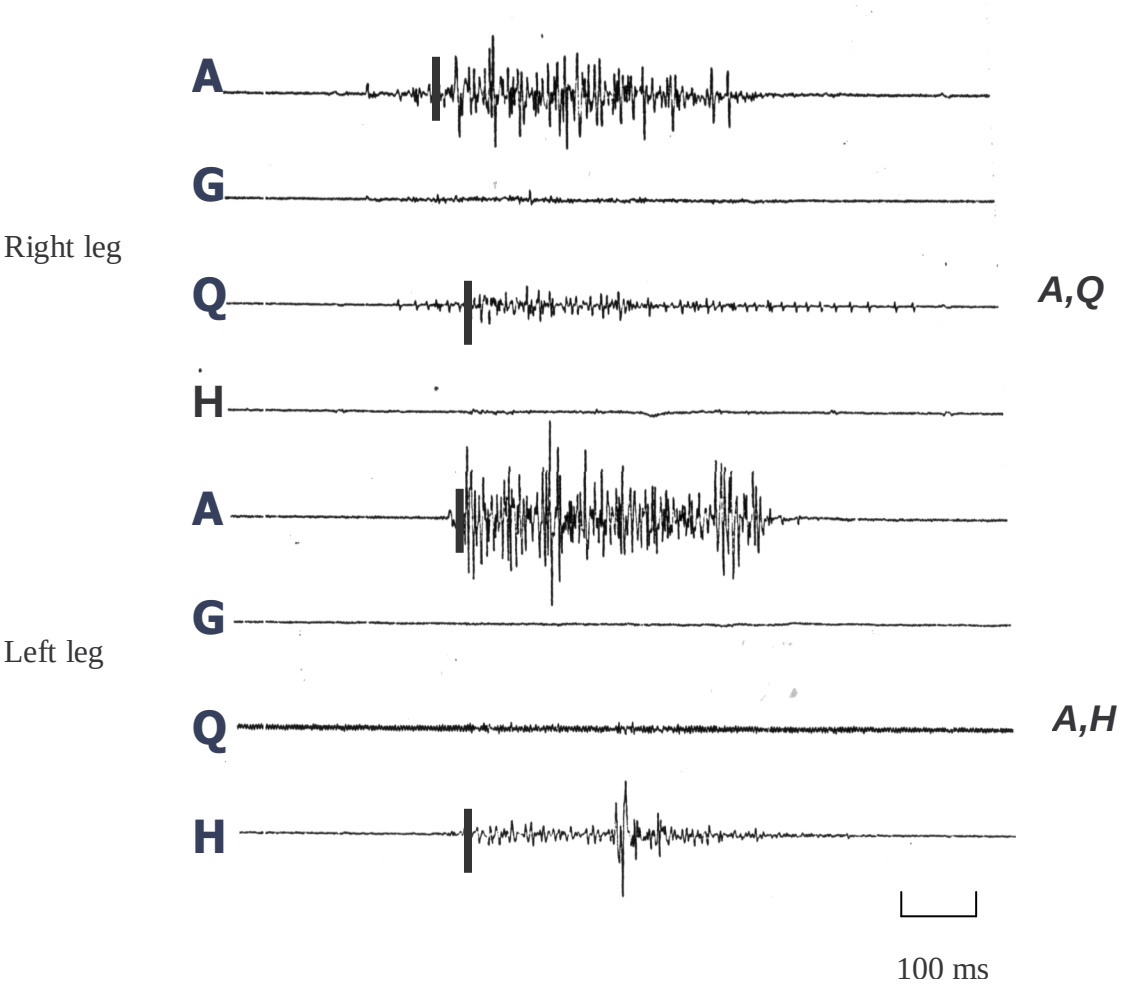

Figure 1. Diagram indicating two EMG assemblies, one on the right leg and the other on the left leg occurring simultaneously. The two legs are analyzed separately. A – anterior tibialis, G – gastrocnemius, Q – quadriceps, H – hamstrings. The short vertical lines represent the start of each EMG activation. Legend to the right of the two assemblies indicates our classification of the two assemblies. The commas between the letters of muscle groups involved are used indicate that the time interval between activations (as indicated by the vertical lines) was less than 50 ms.

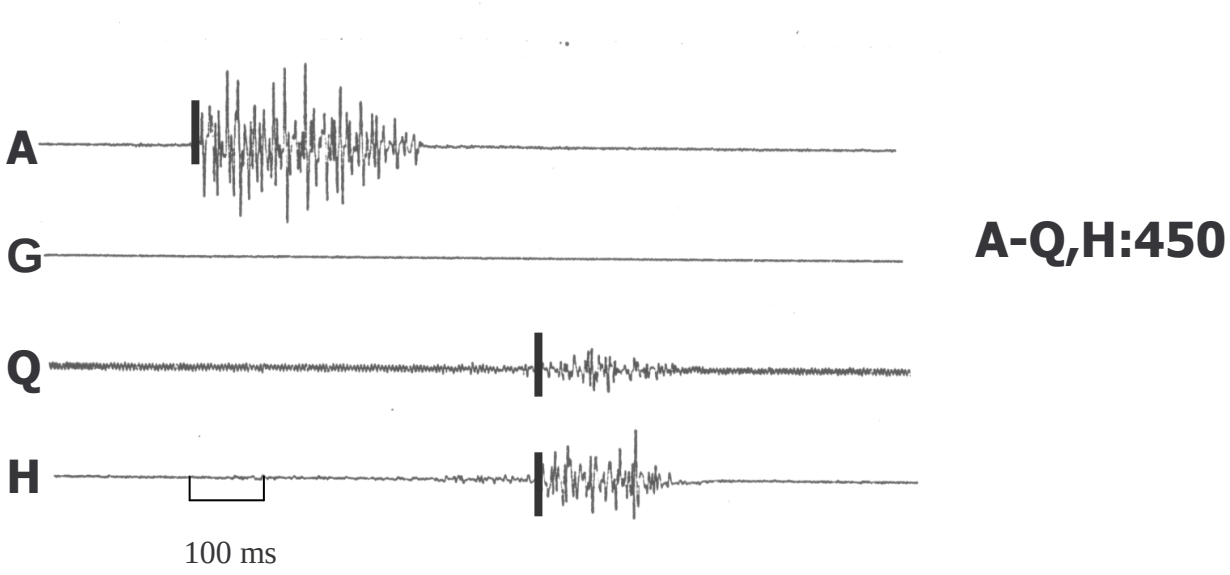

Figure 2. Diagram of an assembly where the delay between activation of two muscle groups is greater than 50 ms. A-anterior tibialis, G-gastrocnemius, Q – quadriceps, H – hamstring. Legend to the right of the assembly indicates our classification: – between letters in the classification indicates the muscle groups involved in the delay. The number after the colon indicates the duration of the assembly between the beginning of the first and the last muscle group activated rounded to the nearest 50 ms.

Age (y)	Gender	Total Sleep Time (h)	Assemblies			Patterns		
			Total	Right leg	Left leg	Total	Right leg	Left leg
64	F	4.1	250	120	130	28	19	13
63	F	3.4	524*	330	194	25	16	14
30	F	5.1	126	57	69	21	11	13
18	F	6.0	367	176	191	39	26	21
59	F	2.7	198	101	97	38	20	23
25	F	7.6	-	61	-	-	29	-
40	M	4.3	40	16	24	2	2	1
45	M	5.3	307*	236	71	33	20	19
68	M	4.4	140*	56	84	22	10	14
45		4.4	198	101	84	25	18	14
(25,64)		(3.4,6.0)	(96,367)	(56,236)	(40,191)	(17,38)	(10,26)	(8,21)

Table 1: Characteristics of subjects recorded for classification of activation patterns. Total sleep time was that recorded on the night in the sleep laboratory. Total number of assemblies and patterns observed are divided into the number observed in right and left legs. * significant difference between number of assemblies in the two legs on binomial distribution. – represents missing data. Medians (95%CI) for the columns indicated on the last row.

	Stage 2 sleep	Slow wave sleep	REM sleep
Assemblies %	72.3* (48.9,79.3)	20.7 (2.5,35.5)	9.1 (1.5,22.7)
Patterns (n)	22.5* (16.0,36.0)	8.0 (3.0,16.0)	9.0 (2.0,23.0)
Unique patterns (n)	12.5 (4.0,21.0)	0.5 (0,5.0)	2.5 (0,9.0)

Table 2. Characteristics of the changes in leg muscle activations during three different sleep stages in eight subjects. Slow wave sleep comprises stage 3 and 4 sleep. Data is calculated for each subject individually and medians calculated for the group. All values expressed as medians (confidence intervals).* $p<0.05$ compared to slow wave sleep and REM sleep.

CHAPTER 8

CONCLUSION

Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLMs) constitute separate sensory and motor conditions which often occur in the same patient. There are specific well-established criteria for diagnosis of both conditions (Allen, Picchietti et al 2003; Zucconi, Ferri et al 2006). Patients are diagnosed and treated for these disorders without sufficient knowledge of the origin and mechanisms involved in the production of the sensory symptoms and / or motor events. In this thesis I have explored some of the qualities of these two disorders specifically looking at possible reasons for the increased prevalence in women as observed in population studies, as well as measurement of the spontaneous sensations and motor events with a particular view to providing a qualitative description for both phenomena.

An increased prevalence of RLS in women has been found in almost all studies which have separated population prevalence by gender (Chapter 1.3). A simple genetic transmission favouring women has not been substantiated by any genetic study, and any other reasons remain under-researched. There are a few possible alternative explanations for the gender bias in RLS including changes in gonadal hormones, a greater impact on sleep continuity, an increased sensitivity to the sensory stimuli and an increased risk in women of conditions which themselves increase the risk of RLS and also have a gender bias.

My first study investigated the impact of a number of factors including genetic transmission, by means of a family history, the impact of RLS on sleep parameters and

the possible gender bias in medical conditions which may precipitate or otherwise be associated with RLS. I asked subjects with RLS who had applied for inclusion in a treatment research protocol to complete a questionnaire. The demographics of the group confirmed the predominance of women as well as a significantly increased number of women relatives of the subjects affected by RLS. Women, when compared to men, were more likely to have a higher symptom load when those symptoms included interference with sleep onset, sleep continuity and involuntary movements while awake. There were also many qualities of RLS unaffected by gender including age of onset of RLS, number of affected days per week, and severity of daytime sleepiness. One hypothesis that women with RLS may have a higher incidence of gender biased co-morbid conditions was borne out only in the higher incidence of hypothyroidism in our women subjects when compared to men.

My data thus do not confirm a primary role for sleep disturbance as a reason for the gender bias in prevalence studies but may indicate a possible role for hypothyroidism. Future studies would need to expand this avenue of research to look at other reasons for the gender difference. More detail need to be obtained on the family histories and pedigrees given by subjects with RLS to investigate the contribution of genetic transmission on the gender bias of RLS. There is still no clarity on the most obvious reasons, that of differing hormonal levels in females with RLS when compared to males with RLS. The results at present are contradictory with periods when oestrogen is high (pregnancy) and periods when oestrogen is low (menopause) both showing high prevalence rates of RLS. The relationship between gender and the medical conditions

associated with RLS particularly those of hypothyroidism, depression and anxiety needs to be explored particularly as far as contributing mechanisms are concerned. Of particular importance is the nature of the relationship and thus, whether these medical disorders are involved in the precipitation of RLS or simply co-exist with RLS. In most cases the prevalence of RLS in other medical conditions, apart from those known to cause RLS such as renal failure and pregnancy, has not been investigated. Even in these established secondary causes, the relationship between RLS and the secondary cause is under researched, particularly as far as their contribution to the gender differences in prevalence studies are concerned.

Another possible reason for the gender bias, mentioned above but not explored by my first study, is that of excessive sensitivity to the sensations by women which may in turn lead to the high symptom load. One proposed origin for the sensations is increased excitability of the nervous system, specifically the spinal cord, creating spontaneous and abnormal sensations (Trenkwalder, and Paulus 2004). Research into the source and quality of the sensations has been compromised by the lack of an assessment tool for the type of sensation found in RLS. The sensations have previously been described as paraesthesias and dysaesthesias but as some of the RLS sensations described do not comply with these definitions the suggestion is that the sensations be referred to as "sensory symptoms" of RLS. There is thus no consensus on the origin of the sensations or what term best describes them.

True paraesthesias and dysaesthesias are usually associated with neuropathic pain (Woolf 2004). There is, however, no qualitative or quantitative validated measure for this type of sensation (Bouhassira et al 2004). There is some evidence to suggest that the sensations of RLS have some features in common with some pain conditions, particularly neuropathic pain, including abnormalities in pain processing, the effectiveness of analgesics in treating the sensations of RLS and evidence for hyperexcitability of the spinal cord in RLS. If RLS is related to pain the evidence from the pain literature tends to indicate that women are more sensitive to pain, both experimental and clinica,l and this difference could then help to explain the higher prevalence of RLS in this gender (Fillingim et al 1999; Unruh 1996).

Thus in an attempt to define the sensations associated with RLS and possibly to link the RLS sensations to those of pain, I investigated whether the sensations of RLS could be measured on a qualitative scale usually used to assess pain – the McGill Pain Questionnaire (MPQ) (Melzack 1975). The MPQ is a validated instrument for measuring both the quality and severity of pain and has been used to compare the words chosen by patients with different types of pain. Severity of pain can also be assessed using two measures calculated from the actual words chosen as well as the total number of words chosen.

We were able to show in 25 patients with RLS that indeed the patients were able to describe their sensations associated with RLS on the MPQ. The severity measures from the actual words and number of words chosen also correlated well with the scores from

the validated IRLSSG RLS severity questionnaire answered by the same patients. There was also a consistency in the words chosen by patients with RLS with eight words chosen by at least 30% of the patients. There was, however, no correlation between the severity scores as calculated from the MPQ or the RLS severity scales and measurements from a visual analogue scale measuring the severity of pain. While this last feature would tend to negate a relationship between the sensations of RLS and those of pain it is not entirely unexpected. While the sensations of RLS are clearly present they are often not painful, the visual analogue scale only measures a quantitative dimension of pain and such a dissociation between the two types of scales has been found previously in mild postoperative pain which may provide a more appropriate comparison to RLS (Katz et al 1994).

The lack of comparable studies analyzing other types of non-painful, but still spontaneous, sensations to compare to those of RLS makes the relationship between the sensations of RLS and other sensations difficult to determine. The next step in this process would be to compare the sensations experienced by patients with RLS to dysaesthesias from other causes, such as diabetic neuropathy. There may also be a difference in the descriptions of sensations experienced by RLS patients who do experience pain and non-painful sensations simultaneously compared with those who only experience non-painful sensations. In those RLS patients who have painful sensations the visual analogue score may correlate better with the MPQ measurements (von Spiczak et al 2005). In order to more precisely determine whether the sensations of RLS are similar to those experienced in neuropathic pain, the answers to the MPQ

questionnaires from RLS patients would need to be compared to subjects with both painful and non-painful sensations associated with neuropathic disorders. Defining the characteristics of the sensations associated with RLS as well as other spontaneous sensations found in other disorders may also increase the therapeutic options for treatment of both disorders.

Thus increased excitability of the nervous system may produce spontaneous sensations but such excitability would also be likely to affect the motor system in the spinal cord. In the case of patients with RLS this motor excitability usually expresses as PLM. These "movements' are currently measured by electromyographic activations from surface EMG recordings over the anterior tibialis muscle (Zucconi et al 2006). The periodic activations known as PLM are common in patients with RLS but occur quite frequently in patients with other sleep disorder as well as in normal elderly subjects without any sleep complaints (Montplaisir et al 2000). The standard recording procedure of only recording one muscle group and limiting the analysis of activation only to those that fit current PLM criteria has provided limited but often contradictory, information. Specifically there are some changes in the PLM with sleep stage but there is a lack of sufficient correlation between PLM and other events during sleep such as arousals and cyclic alternating pattern. These associated events are presumed to produce the clinical impact of PLMs but any such relationship has not been forthcoming. Visual descriptions of the PLM involving multiple muscles were first reported in some of the early studies on PLM yet very few studies have objectively recorded more than one muscle. Various studies have been reported recently but have failed to show any predictable patterning for

the PLM but the use of three different methods of describing the activations and no useful classification system makes comparisons difficult (Provini et al 2001; de Weerd et al 2004; Vetrugno et al 2005; Plazzi et al 2002). The studies were limited by confining their analysis to those activations which fulfilled the current PLM criteria.

In order to provide a means of comparison between muscle activations I wanted to produce a simple, useful classification, using the activations from four muscle groups in the legs to compare PLM activations.

I was able to develop a system of classifying patterns by determining the sequence of muscles involved in the activations as well as measuring the time intervals between activations by recording the leg muscle activations in four muscle groups on each leg in 10 patients with RLS. All activations for each subject were analysed without consideration for their compliance to standard PLM criteria (Zucconi et al 2006).

Initially, I showed that there were 80 unique activation patterns created by the 10 subjects which could be differentiated by sequence or activation intervals and that all muscle groups could be involved in initiation of activations. There were only two patterns, both starting with anterior tibailis, independent of duration, common to all subjects. We confirmed that a technical concern, that of the distance between electrodes created by the anatomical arrangement of muscle groups was not a factor in determining the order of muscle activation. We expected patterns with fewer muscle groups involved to be shorter

in duration, but this was not always so. I also showed for the first time that in most patterns the total time between activations is most likely to be less than 500 ms.

I then used the classification to examine changes in patterning both in uniqueness and inter-activation duration between three different sleep stages. The differences in patterns between sleep stages were subtle. All complexities of pattern were present in all sleep stages but there were significantly more patterns in stage 2 sleep than in slow wave sleep and REM sleep. Each stage of sleep had unique motor patterns. The duration between initiating activations was not changed in two subjects by a change in sleep stage. The data that, in some respects, the motor system behaves very similarly in slow wave sleep and REM sleep is new but may only occur in patients with pathology associated with PLM in patients who have RLS. More research using the classification in patients with other disorders which present with PLM would elucidate the differences in the motor system during different stages of sleep. Very little research has been done on the state (excitability) of the motor system in sleep stages other than REM with the focus on the dramatic atonia during REM sleep (Chase and Morales 2005).

To begin with, the classification needs to be used to compare patterns occurring during PLM periods with those usually left out of the WASM criteria i.e. non-perioidc limb movements in the same patient (Zucconi et al 2006). Given the concern with the lack of relationship between PLM and sleep disruption, a further study could dissect the patterns and relate the individual muscle group activity to time of arousals and cyclic alternating pattern. Another essential comparison to be made is between the patterns of the PLM of

wakefulness and those during sleep in order to determine whether these two phenomena are generated from the same site (Trenkwalder et al 1996).

The search for the origin of the movements may be more complicated given the large number of patterns obtained as the patterns are less likely to come from a single site designated to one specific function e.g. locomotion. There needs to be clarity on whether the simple activations, such as those involving one or two muscle groups, are subsets of the complex activations which would reduce the total number of patterns thus simplifying the search for the generator. My classification could be used in future studies to compare PLM with motor patterns during voluntary movements, particularly locomotion, in order to determine whether the CPGs in the spinal cord are involved in PLM generation. The EMG patterns can also be compared better with other motor events previously suggested to be linked to PLM, such as the Babinski response and the flexor withdrawal reflex (Smith 1985; Bara-Jimenez et al 2000).

With a classification system for the electrical portion of the motor event a further study needs to investigate, using actigraphs, which of the patterns lead to movements, and whether these movements provide a better correlation to clinical symptoms. In itself our classification to divide the activations in patterns, either in number, duration, complexity or combinations of all three may provide information which would correlate better with clinical symptoms than current PLM criteria does. Combining the actigraphy with a more detailed EMG recording such as I have done may well indicate the source of the movements known as PLM. Thus our classification opens the door to more detailed

analysis of leg movements occurring during sleep and wakefulness as well as trying to understand the possible pathological influence they may produce.

In conclusion, many qualities of RLS and PLM remain to be defined. Some of the gender differences found in the disorder on population studies may be explained by the greater impact of the disorder on the sleep of affected women. The use of a validated pain questionnaire to measure the quality and severity of RLS sensations opens the way to a more complete analysis of the sensations. Our new classification of the muscle activations can be used in many ways to improve the analysis of the origin and impact of the muscle activations associated with PLM. Hopefully, the development of these new techniques to analyse RLS and PLM will make the future research into the basic mechanisms behind these two disorders more fruitful in the future.

CHAPTER 9

REFERENCES

Akpinar S (1982). Treatment of restless legs syndrome with levodopa plus benserazide. *Arch Neurol* **39**: 739.

Aksu M, Demirci S and Bara-Jimenez W (2007) Correlation between putative indicators of primary restless legs syndrome severity. *Sleep Med* **8**: 84-9.

Allen RP and Earley C J (2001a). Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol* **18**: 128-47.

Allen RP and Earley CJ (2001b). Validation of the John Hopkins restless legs severity scale. *Sleep Med* 2: 239-42.

Allen RP, Barker PB, Wehrl F, Song HK and Earley CJ (2001). MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* **56**: 263-5.

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS and Montplaisir J (2003). Restless legs syndrome: diagnostic criteria, special considerations and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* **4**: 101-19.

Allen RP (2004). Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med* **5**: 385-91.

Allen RP, Walters AS, Montplaisir J, Hening WA, Myers A, Bell TJ and Ferini-Strambi L (2005) Restless legs syndrome prevalence and impact: REST general population study. *Arch Int Med* **165**: 1286-92.

Allison F (1943). Obscure pains in the chest, back or limbs. *Can Med Assoc J* **48**: 36-8.

Ancoli-Israel S, Kripke DF, Mason W and Kaplan OJ (1985). Sleep apnea and periodic movements in an aging sample. *J Gerontol* **40**: 419-25.

Ancoli-Israel S, Cole R and Alessi C (2003). The role of actigraphy in the study of sleep and circadian rhythms. *Sleep* **26**: 342-92.

Ancoli-Israel S (2005). Actigraphy. *Principles and Practice of Sleep Medicine.* M. H. Kryger, T. Roth and W. Dement. Philadelphia, Elsevier**:** 1459-67.

Anke A, Stenehjem A and Stanghelle J (1995). Pain and quality of life within 2 years of spinal cord injury. *Paraplegia* **33**: 555-9.

Banno K, Delaive K, Walld R and Kryger MH (2000). Restless legs syndrome in 218 patients: associated disorders. *Sleep Med* **1**: 221-9.

Bara-Jimenez W, Aksu M, Graham B, Sato S and Hallett M (2000). Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. *Neurology* **54**: 1609-16.

Barriere G, Cazalets J, Bioulac B, Tison F and Ghorayeb I (2005). The restless legs syndrome. *Prog Neurobiol* **77**: 139-65.

Bartlett G, Stewart J, Tamblyn R and Abrahamowicz M (1998). Normal distributions of thermal and vibration sensory thresholds. *Muscle Nerve* **21**: 367-74.

Beiske A, Pederson E, Czujko B and Myhr K (2004). Pain and sensory complaints in multiple sclerosis. *Eur J Neurol* **11**: 479-82.

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

Beric A, Dimitrijevic M and Lindblom U (1988). Central dysesthesia syndrome in spinal cord injury patients. *Pain* **34**: 109-16.

Bjorvatn B, Leissner L, Ulfberg J, Gyring J, Karlsborg M, Regeur L, Skeidsvoll H, Nordhus I and Pallesen S (2005). Prevalence, severity and risk factors of restless legs syndrome in the general population in two Scandinavian countries. *Sleep Med* **6**: 307-12.

Boivie J (2006). Central pain. *Textbook of Pain*. Eds McMahon and Koltzenburg. Philadelphia, Elsevier**:** 1057-74.

Boivin DB, Lorrain D and Montplaisir J (1993). Effects of bromocriptine on periodic limb movements in human narcolepsy. *Neurology* **43**: 2134-6.

Bonati M T, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M and Casari, G (2003). Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain* **126**: 1485-92.

Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquielier E, Rosataing S, Lanteri-Minet M, Collin E, Grisart J and Boureau F (2004). Development and validation of the Neuropathic Pain Symptoms Inventory. *Pain* **108**: 248-57.

Brown LK, Heffner JE and Obbens EA (2000). Transverse myelitis associated with restless legs syndrome and periodic movements of sleep responsive to an oral dopaminergic agent but not to intrathecal baclofen. *Sleep* **23**: 591-4.

Brown LK, Dedrick DL, Doggett JW and Guido PS (2005). Antidepressant medication use and restless legs syndrome in patients presenting with insomnia. *Sleep Med* **6**: 443-50.

Bucher SF, Seelos KC, Oertel WH, Reiser M and Trenkwalder C (1997). Cerebral generators involved in the pathogenesis of the restless legs syndrome. *Ann Neurol* **41**: 639-45.

Camhi S, Morgan W, Pernisco N and Quan S (2000). Factors affecting sleep disturbance in children and adolescents. *Sleep Med* **1**: 117-23.

Capaday C (2002). The special nature of human walking and its neural control. *TINS* **25**: 370-6.

Carrier J, Frenette S, Montplaisir J, Paquet J, Drapeau C and Morettini J (2005). Effects of periodic leg movements during sleep in middle-aged subjects without sleep complaints. *Mov Disord*. **20:** 1127-32.

Chase M and Morales F (2005). The control of motorneurones during sleep. *Principles and Practice of Sleep Medicine*. Eds M. Kryger, T. Roth and W. Dement. Philadelphia, Elsevier**:** 104-20.

Chen S, Ondo WG, Rao S, Li L, Chen Q and Wang Q (2004). Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p. *Am J Hum Genet* 74: 876-85.

Chevalier H, Los F, Boichut D, Bianchi M, Nutt D, Hajak G, Hetta J, Hoffmann G and Crowe C (1999). Evaluation of severe insomnia in the general population: results of a European multinational survey. *J Psychopharmacol* **13**: S21-4.

Coccagna G, Vetrugno R, Lombardi C and Provini F (2004). Restless legs syndrome: an historical note. *Sleep Med* **5**: 279-83.

Coleman RM, Pollack CP and Weitzman ED (1980). Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. *Ann Neurol* **8**: 416-21.

Coleman RM (1982). Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. *Sleep and Waking: Indications and techniques*. Ed C. Guilleminault. Menlo Park, Addison-Wesley**:** 265-95.

Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG and Earley CJ (2003). Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology* **61**: 304-9.

Craig M, Cutter W, Wickham H, van Amelsvoort T, Rymer J, Whitehead M and Murphy D (2004). Effect of long-term estrogen therapy on dopaminergic responsivity in post-menopausal women – a preliminary study. *Psychoneuroendocrinology* **29**: 1309-16.

Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, Serra J and Jensen T (2004). EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* **11**: 153-62.

de Weerd A, Rijsman R and Brinkley A (2004). Activity patterns of leg muscles in periodic limb movement disorder. *J Neurol Neurosurg Psychiatry* **75:** 317-9.

Devor M (2006). Sodium channels and mechanisms of neuropathic pain. *J Pain* **15**: S3-S12.

Desautels A, Turecki G, Montplaisir J, Brisebois K, Sequeira A, Adam B and Rouleau G (2002). Evidence for a genetic association between monoamine oxidase A and restless legs syndrome. *Neurology* **59**: 215-9.

Desautels A, Turecki G, Montplaisir J, Xiong L, Walters AS, Ehrenberg BL, Brisebois K, Desautels AK, Gingras Y, Johnson WG, Lugaresi E, Coccagna G, Picchietti DL, Lazzarini A and Rouleau GA (2005). Restless legs syndrome: confirmation of linkage to chromosome 12q, genetic heterogeneity, and evidence of complexity. *Arch Neurol* **62**: 591-6.

Dickel MJ and Mosko SS (1990). Morbidity cut-offs for sleep apnea and periodic leg movements in predicting subjective complaints in seniors. *Sleep* **13**: 155-66.

Dickel MJ, Renfrow SD, Moore PT and Berry RB (1994). Rapid eye movement sleep periodic leg movements in patients with spinal cord injury. *Sleep* **17**: 733-8.

Dietz V (2003). Spinal cord pattern generators for locomotion. *Clin Neurophys* **114**: 1379-89.

Ditunno J, Little J, Tessler A and Burns A (2004). Spinal shock revisited: a four phase-model. *Spinal Cord* **42**: 383-95.

Dorsey C, Lukas S and Cunningham S (1996). Fluoxetine-induced sleep disturbance in depressed patients. *Neuropsychopharmacology* **14**: 437-442.

Dubuisson D and Melzack R (1976). Classification of clinical pain descriptors by multiple group discriminant analysis. *Exp Neurol* **51**: 480-487.

Earley CJ, Heckler D and Allen RP (2004). The treatment of RLS with intravenous iron dextran. *Sleep Med* **5**: 231-5.

Edinger JD (2003). Cognitive and behavioral anomalies among insomnia patients with mixed restless legs and periodic limb movement disorder. *Behav Sleep Med* **1**: 37-53.

Ekbom K (1945). Restless legs: clinical study of hitherto overlooked disease in legs characterised by peculiar paresthesia ('Anxietas Tibiarum'), pain and weakness and occurring in two main forms, asthenia crurum paraesthetica and asthenia crurum dolorosa; short review of paresthesias in general. *Acta Med Scand* **158**: 1-123.

Esteves AM, de Mello MT, Lancellotti CL, Natal CL and Tufik S (2004). Occurrence of limb movement during sleep in rats with spinal cord injury. *Brain Res* **1017**: 32-8.

Farina D, Merletti R and Enoka RM (2004). The extraction of neural strategies from the surface EMG. *J Appl Physiol* **96**: 1486-95.

Feine J, Bushnell M, Miron D and Duncan G (1991). Sex differences in the perception of noxious heat stimuli. *Pain* **44**: 255-262.

Ferri R, Zucconi M, Manconi M, Bruni O, Miano S, Plazzi G and Ferini-Strambi L (2005). Computer-assisted detection of nocturnal leg motor activity in patients with restless legs syndrome and periodic leg movements during sleep. *Sleep* **28**: 998-1004.

Fillingim R, Edwards R and Powell T (1999). The relationship of sex and clinical pain to experimental pain responses. *Pain* **83**: 419-25.

Finnerup N, Johannesen I, Fuglsang-Frederickson A, Bach F and Jensen T (2003). Sensory function in spinal cord injury patients with and without central pain. *Brain Res* **126**: 57-70.

Fitzpatrick, P. (1989). The metal requirements of rat tyrosine hydroxylase. *Biochem Biophys Res Commun* **161**: 211-5.

Frymoyer J W (1994). Degenerative Spondylolisthesis: Diagnosis and Treatment. *J Am Acad Orthop Surg* **2**: 9-15.

Fujiki A, Shimizu A, Yamada Y, Yamamoto J and Kaneko Z (1971). The Babinski reflex during sleep and wakefulness. *Electroencephalogr Clin Neurophysiol* **31**: 610-3.

Galofre J, Garcia-Mayor R, Fluiters E, Fernandez-Calvet L, Rego A, Paramo C and Andrade M (1994). Incidence of different forms of thyroid dysfunction and its degrees in an iodine sufficient area. *Thyroidology* **6**: 49-54.

Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X and Hernandez G (2002). Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* **59**: 1573-9.

Garcia-Borreguero D, Larrosa O, de la Llave Y, Jose Granizo J and Allen RP (2004). Correlation between rating scales and sleep laboratory measurements in restless legs syndrome. *Sleep Med* **5**: 561-5.

Garcia-Borreguero D, Egatz R, Winkelmann J, and Berger K (2006) Epidemiology of restless legs syndrome: The current status. *Sleep Med Rev* **10**: 153-167.

Gigli G, Adorati M, Dolso P, Piani A, Valente M, Brotini S and Budai R (2004). Restless legs syndrome in end-stage renal disease. *Sleep Med* **5**: 309-15.

Grillner S (1985). Neurobiological bases of rhythmic motor acts in vertebrates. *Science* **228**: 143-9.

Grillner S, Hellgren J, Ménard A, Saitoh K and Wikström MA (2005). Mechanisms for selection of basic motor programs – roles for the striatum and pallidum. *TINS* **28**: 364-370.

Gschliesser V, Brandauer E, Ulmer H, Poewe W and Hogl B (2006). Periodic limb movement counting in polysomnography: Effects of amplitude. *Sleep Med* **7**: 249-54.

Guilleminault C, Raynal D, Weitzman E and Dement WC (1975). Sleep-related periodic myoclonus in patients complaining of insomnia. *Trans Am Neurol Assoc* **100**:

19-22.

Haba-Rubio J, Staner L, Krieger J and Macher JP (2005). Periodic limb movements and sleepiness in obstructive sleep apnea patients. *Sleep Med* **6**: 225-9.

Hendricks V, Altshuler L and Suri R (1998). Hormonal changes in the postpartum and implications for postpartum depression. *Psychosomatics* **39**: 93-101.

Hening WA, Walters AS, Wagner M, Rosen R, Chen V, Kim S, Shah M and Thai O (1999). Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. *Sleep* **22**: 901-12

Hening WA, Walters AS., Allen RP, Montplaisir J, Myers A and Ferini-Strambi L (2004a). Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* **5**: 237-46.

Hening WA, Allen RP, Earley CJ, Picchietti DL and Silber MH (2004b). An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* **27**: 560-83.

Hess S, Zimmermann M, Arnold M, Langhans W and Hurrell R (2002). Iron deficiency anemia reduced thyroid peroxidase activity in rats. *J Nutr* **132**: 1951-5.

Hornyak M, Kopasz M, Feige B, Riemann D and Voderholzer U (2005). Variability of periodic leg movements in various sleep disorders: implications for clinical and pathophysiologic studies. *Sleep* **28**: 331-5.

Hornyak M, Feige B, Riemann D and Voderholzer U (2006). Periodic leg movements in sleep and periodic limb movement disorder: Prevalence, clinical significance and treatment. *Sleep Med Rev* **10**: 169-177.

Houck J (2003). Muscle activation patterns of selected lower extremity muscles during stepping and cutting tasks. *J Electromyogr Kines* **13**: 545-54.

ICSD – International classification of sleep disorders: Diagnostic and coding manual. Diagnostic Classification Steering Committee, Thorpy MJ, Chairman. Rochester, Minnesota: American Sleep Disorders Association, 1990.

Ivanenko Y, Poppele R and Lacquaniti F (2004). Five basic muscle activation patterns account for muscle activity during human locomotion. *J Physiol* **556**: 267-82.

Johnson M (1997). The physiology of the sensory dimensions of clinical pain. *Physiotherapy* **83**: 526-36.

Kageyama T, Kabuto M, Nitta H, Kurokawa Y, Taira K, Suzuki S and Takemoto T (2000). Prevalences of periodic limb movement-like and restless legs-like symptoms among Japanese adults. *Psych Clin Neurosci* **54**: 296-298.

Kandel E, Schwartz J and Jessel T (2000). *Principles of Neural Science.* New York, McGraw-Hill.

Karadeniz D, Ondze B, Besset A and Billiard M (2000). EEG arousals and awakenings in relation with periodic leg movements during sleep. *J Sleep Res* **9**: 273-7.

Katz J, Clairoux M, Kavanagh B, Roger S, Nierenberg H, Redahan C and Sandler AN (1994). Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient controlled morphine consumption after lower abdominal surgery. *Pain* **59**: 395-403.

Katz J and Melzack R (1991) Auricular TENS reduces phantom limb pain. *J Pain Symptom Manage* **6**: 73-83.

Kazenwadel J, Pollmacher T, Trenkwalder C, Oertel WH, Kohnen R, Kunzel M and Kruger HP (1995). New actigraphic assessment method for periodic leg movements (PLM). *Sleep* **18**: 689-97.

Keogh E and Herdenfeldt M (2002). Gender, coping and the perception of pain. *Pain* **97**: 195-201.

King M, Jaffre M, Morrish E, Shneerson J and Smith I (2005). The validation of a new actigraphy system for measurement of periodic limb movements during sleep. *Sleep Med* **6**: 507-13.

Kryger MH, Otake K and Foerster J (2002). Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers. *Sleep Med* **3**: 127-32.

Lavigne GJ and Montplaisir JY (1994). Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. *Sleep* **17**: 739-43.

Lazzarini A, Walters AS, Hickey K, Coccagna G, Lugaresi E, Ehrenberg BL, Picchietti DL, Brin MF, Stenroos ES, Verrico T and Johnson WG (1999). Studies of penetrance and anticipation in five autosomal-dominant restless legs syndrome pedigrees. *Mov Disord* **14**: 111-6.

Lee KA, McEnany G and Weekes D (1999). Gender differences in sleep patterns for early adolescents. *J Adolesc Health* **24**:16-20.

Lee KA, Zaffke ME and Baratte-Beebe K (2001). Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gend Based Med* **10**: 335-41.

Lee MS, Choi YC, Lee SH and Lee SB (1996). Sleep-related periodic leg movements associated with spinal cord lesions. *Mov Disord* **11**: 719-22.

Lee PH, Lee JS, Yong SW and Huh K (2005). Repetitive involuntary leg movements in patients with brainstem lesions involving the pontine tegmentum: evidence for a pontine inhibitory region in humans. *Parkinsonism Relat Disord* **11**: 105-10.

Leranth C, Roth RH, Elsworth JD, Naftolin F, Horvath TL and Redmond DE (2000). Estrogen is essential for maintaining nigrostriatal dopamine neurons in primates: Implications for Parkinson's disease and memory. *J Neurosci* **20**: 8604-9.

Lesage S and Hening WA (2004). The restless legs syndrome and periodic limb movement disorder: a review of management. *Semin Neurol* **24**: 249-59.

Leutgeb U and Martus P (2002). Regular intake of non-opioid analgesics is associated with an increased risk of restless legs syndrome in patients maintained on antidepressants. *Eur J Med Res* **7**: 368-78.

Levenson C and Fitch C (2000). Effect of altered thyroid hormone status on rat brain ferritin H and ferritin L mRNA during postnatal development. *Brain Res Dev Brain Res* **119**: 105-9.

Li R, Wing Y, Ho S and Fong S (2002). Gender differences in insomnia - a study in the Hong Kong Chinese population. *J Psychosom Res* **53**: 601-9.

Lindsell C and Griffin M (2003). Normative vibrotactile thresholds measured at five European test centres. *Int Arch Occup Environ Health* **76**: 517-28.

Lugaresi E, Tassinari C, Coccagna G and Ambrosetto C (1965). Particularites cliniques et polygraphiques du syndrome d'impatience des membres inferieurs. *Rev Neurol (Paris)* **113**: 545-55.

Lugaresi E, Coccagna G, Gambi D, Berti-Ceroni G and Poppi M (1966). A propos de quelques manifestatons nocturnes myocloniques (Nocturnal Myoclonus de Symonds). *Rev Neurol (Paris)* **115**: 547-55.

Mahowald MW (2001). Con: assessment of periodic leg movements is not an essential component of an overnight sleep study. *Am J Respir Crit Care Med* **164**: 1340-1; discussion 1341-2.

Manber R and Armitage R. (1999). Sex, sleep and steroids. *Sleep* **22**: 540-561.

Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, Mollica G, Ferini-Strambi L and Granieri E (2004). Restless legs syndrome and pregnancy. *Neurology* **63**: 1065-9.

Martinelli P, Coccagna G and Lugaresi E (1987). Nocturnal myoclonus, restless legs syndrome, and abnormal electrophysiological findings. *Ann Neurol* **21**: 515.

Mathie M, Coster A, Lovell N and Celler B (2004). Accelerometry: providing an integrated, practical method for long-term, ambulatory monitoring of human movement. *Physiol Meas* **25**: R1-20.

Meh D and Denislic M (1995). Influence of age, temperature, sex, height and diazepam on vibration perception. *J Neurol Sci* **134**: 136-42.

Melzack R (1975). The McGill pain questionnaire. *Pain* **1**: 277-299.

Melzack R and Katz J (2006). Pain assessment in adult patients. *Textbook of Pain.* Eds McMahon and Koltzenburg. Elsevier: Philadelphia. p. 291-304.

Mendelson WB (1996). Are periodic leg movements associated with clinical sleep disturbance? *Sleep* **19**: 219-23.

Merskey H (1991). The definition of pain. *Eur J Psychiatry* **6**: 153-59.

Meyer R, Ringkamp M, Campbell J and Raja S (2006). Peripheral mechanisms of cutaneous nociception. *Textbook of Pain* Eds McMahon and Koltzenburg. Elsevier: Philadelphia. p. 3-34.

Michaud M, Poirier G, Lavigne G and Montplaisir J (2001). Restless Legs Syndrome: scoring criteria for leg movements recorded during the suggested immobilization test. *Sleep Med* **2**: 317-21.

Michaud M, Lavigne G, Desautels A, Poirier G and Montplaisir J (2002a). Effects of immobility on sensory and motor symptoms of restless legs syndrome. *Mov Disord* **17**: 112-5.

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

Michaud M (2006). Is the suggested immobilization test the “gold standard” to assess restless legs syndrome? *Sleep Med* **7**: 541-3.

Micó J, Ardid D, Berrocoso E, Eschalier A (2006). Antidepressants and pain. *TIPS* **27**: 348-54.

Milligan SA and Chesson AL (2002). Restless legs syndrome in the older adult: diagnosis and management. *Drugs Aging* **19**: 741-51.

Minassian K, Jilge B, Rattay F, Pinter MM, Binder H, Gerstenbrand F and Dimitrijevic MR (2004). Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound action potentials. *Spinal Cord* **42**: 401-416.

Mizuno S, Miyaoka T, Inagaki T, and Horiguchi J (2005a). Prevalence of restless legs syndrome in non-institutionalized Japanese elderly. *Psychiatry Clin Neurosci* **59**: 461-5.

Mizuno S, Mihara T, Miyaoka T, Inagaki T and Horiguchi J (2005b). Csf iron, ferritin and transferrin levels in restless legs syndrome. *J Sleep Res* **14**: 43-7.

Montplaisir J and Godbout R (1986). Nocturnal sleep of narcoleptic patients. *Sleep* **9**: 159-61.

Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O and Lesperance P (1997). Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord* **12**: 61-5.

Montplaisir J, Boucher S, Nicolas A, Lesperance P, Gosselin A, Rompre P and Lavigne G (1998). Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. *Mov Disord* **13**: 324-9.

Montplaisir J, Michaud M, Denesle R and Gosselin A (2000). Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. *Sleep Med* **1**: 163-7.

Montplaisir J, Allen R, Walters A and Ferini-Strambi L (2005). Restless Legs Syndrome and Periodic Limb Movements during sleep. *Principles and Practice of Sleep Medicine*. Eds M. Kryger, T. Roth and W. C. Dement. Philadelphia, Elsevier**:** 839-52.

Morell R, Prielipp R, Harwood T, James R and Butterworth J (2003). Men are more susceptible than women to direct pressure on unmyelinated ulnar nerve fibers. *Anesth Analg* **97**: 1183-8.

Nichols D, Allen R, Grauke J, Brown J, Rice M, Hyde P, Dement W and Kushida C (2003). Restless Legs Syndrome symptoms in primary care. *Arch Intern Med* **163**: 2323-9.

Nora D, Becker J, Ehlers J and Gomes I (2005). What symptoms are truly caused by median nerve compression in carpal tunnel syndrome? *Clin Neurophysiol* **116**: 275-83.

O'Keeffe ST, Gavin K and Lavan JN (1994). Iron status and restless legs syndrome in the elderly. *Age Ageing* **23**: 200-3.

O'Keeffe S (2005). Secondary causes of restless legs syndrome in older people. *Age Ageing* **34**: 349-52.

Obeso J, Rodrigues-Oroz M, Rodriguez M, Arbizu J and Giménez-Amaya J (2002) The basal ganglia and disorders of movement: Pathophysiological mechanisms. *News Physiol Sci* **17** 51-5.

Ohayon M and Roth T (2002). Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res* **53**: 547-54.

Ohtani H, Nomoto M and Douchi T (2001). Chronic estrogen treatment replaces striatal dopmainergic function in ovariectomized rats. *Brain Res* **900**: 163-8.

Pallesen S, Nordhus I, Nielsen G, Havik O, Kvale G, Johnsen B and Skjotskift S (2001). Prevalence of insomnia in the adult Norwegian population. *Sleep* **24**: 771-9.

Parker G and Hadzi-Pavlovic D (2004). Is the female preponderance in major depression secondary to a gender difference in specific anxiety disorders? *Psychol Med* **34**: 461-70.

Pelland L and McKinley P (2004). A pattern recognition technique to characterise the differential modulation of co-activating muscles at the performer/environmental interface. *J Electromyogr Kinesiol* **14**: 539-54.

Phillips B, Young T, Finn L, Asher K, Hening WA and Purvis C (2000). Epidemiology of restless legs symptoms in adults. *Arch Intern Med* **160**: 2137-41.

Piccinelli M and Wilkinson G (2000). Gender differences in depression. *Br J Psych* **177**: 486-92.

Plazzi G, Vetrugno R, Meletti S and Provini F (2002). Motor pattern of periodic limb movements in sleep in idiopathic RLS patients. *Sleep Med* **3**: S31-34.

Popat RA, Van Den Eeden SK, Tanner CM, McGuire V, Bernstein AL, Bloch DA, Leimpeter A, Nelson LM (2005). Effect of reproductive factors and postmenopausal hormone use on the risk of Parkinson disease. *Neurology* **65:** 383-90

Provini F, Vetrugno R, Meletti S, Plazzi G, Solieri L, Lugaresi E, Coccagna G and Montagna P (2001). Motor pattern of periodic limb movements during sleep. *Neurology* **57**: 300-4.

Riemann D and Voderholzer U (2003). Primary insomnia: a risk factor to develop depression. *J Affect Disorders* **76**: 255-9.

Rijsman R, Neven AK, Graffelman W, Kemp B and de Weerd A (2004). Epidemiology of restless legs in The Netherlands. *Eur J Neurol* **11**: 607-11.

Rizzo M, Kocsis J and Waxman S (1996). Mechanisms of paresthesia, dysesthesia and hyperesthesia: role of Na+ channel heterogeneity. *Eur J Neurol* **36**: 3-12.

Rosenthal T, Bryant E and Lemmi H (1994). Gender differences dominate sleep disorder patients' body problem complaints. *Arq Neuropsiquiatr* **52**: 471-5.

Rothdach AJ, Trenkwalder C, Haberstock J, Keil U and Berger K (2000). Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. *Neurology* **54**: 1064-8.

Rushton D, Dover R, Sainsbury A, Norris M, Gilkes J and Ramsay I (2001). Why should women have lower reference limits for haemoglobin and ferritin concentrations than men? *BMJ.* **322**: 1355-7.

Saletu M, Anderer P, Saletu B, Lindeck-Pozza L, Hauer C and Saletu-Zyhlarz G (2002). EEG mapping in patients with restless legs syndrome as compared with normal controls. *Psychiatry Res* **115**: 49-61.

San Pedro EC, Mountz JM, Mountz JD, Liu HG, Katholi CR and Deutsch G (1998). Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus, and anterior cingulate gyrus. *J Rheumatol* **25**: 2270-5.

Sanders P, Waddy H and Thompson P (1999). An 'annoying' foot: unilateral painful legs and moving toes syndrome. *Pain* **82**: 103-4.

Sarlani E and Greenspan J (2002). Gender differences in temporal summation of mechanically evoked pain. *Pain* **97**: 163-169.

Saunders-Pullman R, Gordon-Elliot J, Parides M, Fahn S, Saunders HR and Bressman S (1999). The effect of estrogen replacement in early Parkinson's disease. *Neurology* **52**:1417-21.

Sawada H and Shimohama S (2000). Neuroprotective effects of estradiol in mesencephalic dopaminergic neurons. *Neurosci Biobehav Rev* **24**: 143-7.

Schenck C and Mahowald M (1990). Polysomnographic, neurologic, psychiatric and clinical outcome report on 70 consecutive cases with REM behaviour disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 cases. *Cleve Clin J Med* **57 Suppl**: S9-S23.

Selden S. (2004) Tickle. *J Am Acad Dermatol* **50**: 93-7.

Seliger S, Davis C and Stehman-Breen C (2001). Gender and the progression of renal disease. *Curr Opin Nephrol Hypertens* **10**: 219-25.

Sevim S, Dogu O, Camdeviren H, Bugdayci R, Sasmaz T, Kaleagasi H, Aral M and Helvaci I (2003). Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. *Neurology* **61**: 1562-9.

Sevim S, Dogu O, Kaleagasi H, Aral M, Metin O and Camdeviren H (2004). Correlation of anxiety and depression symptoms in patients with restless legs syndrome: a population based survey. *J Neurol Neurosurg Psychiatry* **75**: 226-30.

Siddall P and McClelland J (2006). Non-painful sensory phenomena after spinal cord injury. *J Neurol Neurosurg Psych* **66**: 617-22.

Silbiger S and Neugarten J (2003) The role of gender in the progression of renal disease. *Adv Ren Replace Ther* **10**: 3-14.

Silverstein B (2002). Gender differences in the prevalence of somatic versus pure depression: a replication. *Am J Psychiatry* **159**: 1051-2.

Sindrup S and Jensen T (1999). Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* **83**: 389-400.

Sindrup S and Jensen T (2001). Antidepressants in the treatment of neuropathic pain. *Neuropathic pain: Pathophysiology and Treatment* Eds Hansson, P, Fields, H, Hill, R and Marchettini, P. Progress in pain research and management vol 21. IASP Press. Seattle. 169-85.

Smith RC (1985). Relationship of periodic movements in sleep (nocturnal myoclonus) and the Babinski sign. *Sleep* **8**: 239-43.

Smith RC (1987). Confirmation of Babinski-like response in periodic movements in sleep (nocturnal myoclonus). *Biol Psych* **22**: 1271-3.

Stiasny K, Oertel WH and Trenkwalder C (2002). Clinical symptomatology and treatment of restless legs syndrome and periodic limb movement disorder. *Sleep Med Rev* **6:** 253-65.

Stiasny-Kolster K, Magerl W, Oertel WH, Moller JC and Treede RD (2004). Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. *Brain* **127**: 773-82.

Suzuki R, Rygh L and Dickenson A (2004). Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *TIPS* **25**: 613-7.

Symonds C (1953). Nocturnal myoclonus. *J Neurol Neurosurg Psychiatry* **16**: 166-71.

Tan EK, Seah A, See SJ, Lim E, Wong MC and Koh KK (2001). Restless legs syndrome in an Asian population: A study in Singapore. *Mov Disord* **16**: 577-9.

The ASDA Atlas Task Force (1993). Recording and scoring Leg Movements. *Sleep* **16**: 749-59.

Tison F, Crochard A, Leger D, Bouee S, Lainey E and El Hasnaoui A (2004). Epidemiology of restless legs syndrome in French adults: a nationwide survey: the INSTANT study. *Neurology* **65**: 239-46.

Thorpy M (2000). Restless Legs Syndrome: Detection and management in primary care. NIH, *US Department of Health and Human Services*. NIH Publication no.00-3788.

Tracey I (2005). Nociceptive processing in the human brain. *Curr Opin Neurobiol* **15**: 478-87.

Trenkwalder C, Bucher SF and Oertel WH (1996a). Electrophysiological pattern of involuntary limb movements in the restless legs syndrome. *Muscle Nerve* **19**: 155-62.

Trenkwalder C, Seidel VC, Gasser T and Oertel WH (1996b). Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. *Mov Disord* **11**: 389-94.

Trenkwalder C, Hening WA, Walters AS, Campbell SS, Rahman K and Chokroverty S (1999). Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. *Mov Disord* **14**: 102-10.

Trenkwalder C and Paulus W (2004). Why do restless legs occur at rest?-pathophysiology of neuronal structures in RLS. Neurophysiology of RLS (part 2). *Clin Neurophysiol* **115**: 1975-88.

Tribl GG, Sycha T, Kotzailias N, Zeitlhofer J and Auff E (2005). Apomorphine in idiopathic restless legs syndrome: an exploratory study. *J Neurol Neurosurg Psychiatry* **76**: 181-5.

Ulfberg J, Nystrom B, Carter N and Edling C (2001a). Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord* **16**: 1159-63.

Ulfberg J, Nystrom B, Carter N and Edling C (2001b). Restless Legs Syndrome among working women. *Eur Neurol* **46**: 17-9.

Unruh A (1996). Gender variations in clinical pain experience. *Pain* **65**: 123-167.

Van Emmerik R and Wagener R (1996). Dynamics of movement coordination and tremor during gait in Parkinson's disease. *Hum Mov Sci* **15**: 203-35.

Voderholzer U, Al-Shajlawi A, Weske G, Feigi B and Rjemann D (2003). Are there gender differences in objective and subjective sleep measures? A study of insomniacs and healthy controls. *Depress Anxiety* **17**: 162-72.

von Spiczak S, Whone AL, Hammers A, Asselin MC, Turkheimer F, Tings T, Happe S, Paulus W, Trenkwalder C, Brooks DJ (2005).The role of opioids in restless legs syndrome: an [11C]diprenorphine PET study. *Brain*. **128**:906-17.

Walker J and Carmody J (1998). Experimental pain in healthy human subjects: Gender differences in nociception and in response to Ibuprofen. *Anesth Analg* **86**: 1257-62.

Walters AS, Hening W, Rubinstein M and Chokroverty S (1991). A clinical and polysomnographic comparison of neuroleptic-induced akathisia and the idiopathic restless legs syndrome. *Sleep* **14**: 339-45.

Walters AS, Wagner ML, Hening WA, Grasing K, Mills R, Chokroverty S and Kavey N (1993). Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep* **16**: 327-32.

Walters AS (1995). Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord* **10**: 634-42.

Walters AS, Wagner M and Hening WA (1996). Periodic limb movements as the initial manifestation of restless legs syndrome triggered by lumbosacral radiculopathy. *Sleep* **19**: 825-6.

Walters AS, Winkelmann J, Trenkwalder C, Fry JM, Kataria V, Wagner M, Sharma R, Hening WA and Li L (2001). Long-term follow-up on restless legs syndrome patients treated with opioids. *Mov Disord* **16**: 1105-9.

Walters AS, LeBrocq C, Dhar A, Hening WA Rosen R, Allen RP and Trenkwalder C (2003). Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* **4:** 121-132.

Ward D, Evensen K, Vaughn A, Rodgers A and Troiano R (2005). Accelerometer use in physical activity: best practices and research recommendations. *Med Sci Sports Exerc* **37**: S582-8.

Warnes H, Dinner D, Kotagal P and Burgess R (1993). Periodic limb movements and sleep apnoea. *J Sleep Res* **2**: 38-44.

Watanabe S, Sakai K, Ono Y, Seino H and Naito H (1987). Alternating periodic leg movement induced by spinal anesthesia in an elderly male. *Anesth Analg* **66**: 1031-2.

Watanabe S, Ono A and Naito H (1990). Periodic leg movements during either epidural or spinal anesthesia in an elderly man without sleep-related (nocturnal) myoclonus. *Sleep* **13**: 262-6.

Wetter TC and Pollmacher T (1997). Restless legs and periodic leg movements in sleep syndromes. *J Neurol* **244**: S37-45.

Wetter TC, Collado-Seidel V, Oertel H, Uhr M, Yassouridis A and Trenkwalder C. (2002). Endocrine rhythms in restless legs syndrome.*J Neurol* **249**: 146-51.

Winkelmann JW, Chertow GM and Lazarus JM (1996). Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* **28**: 372-8.

Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A and Trenkwalder C (2000). Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep* **23**: 597-602.

Winkelmann J (2002). The genetics of restless legs syndrome. *Sleep Med* **3 Suppl**: S9-12.

Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, Strohle A, Eisensehr I, Dichgans M, Gasser T and Trenkwalder C (2002a). Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. *Ann Neurol* **52**: 297-302.

Winkelmann J, Stautner A, Samtleben W and Trenkwalder C (2002b). Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. *Mov Disord* **17**: 1072-6.

Winkelmann J, Prager M, Lieb R, Pfister H, Spiegel B, Wittchen HU, Holsboer F, Trenkwalder C and Strohle A (2005). "Anxietas tibiarum". Depression and anxiety disorders in patients with restless legs syndrome. *J Neurol* **252**: 67-71.

Winkelmann J and Ferini-Strambi L (2006). Genetics of restless legs syndrome. *Sleep Med Rev* **16**: 179-183.

Winter D and Yack H (1987). EMG profiles during normal human walking: stride-to-stride and inter-subject variability. *Electroencephalogr Clin Neurophysiol* **67**: 402-11.

Wong DF, Broussolle EP, Wand G, Villemagne V, Dannals RF, Links JM, Zacur HA, Harris J, Naidu S, Braestrup C, Wagner HN and Gjedde A (1988). In vivo measurement of dopamine receptors in human brain by positron emission tomography. Age and sex difference. *Ann NY Acad Sci* **515**: 203-14.

Woolf C (2004). Dissecting out mechanisms responsible for neuropathic pain: Implications for diagnosis and therapy. *Life Sciences* **74**: 2605-10.

Wright K, Asmundsen G and McCreary D (2001). Factorial validity of the short-form McGill pain questionnaire (SF-MPQ). *Eur J Pain* **5**: 279-84.

Yokota T, Hirose K, Tanabe H and Tsukagoshi H (1991). Sleep-related periodic leg movements (nocturnal myoclonus) due to spinal cord lesion. *J Neurol Sci* **104**: 13-8.

Zaremba P, Bialek M, Blaszczyk B, Cioczek P and Czuczwar S (2006). Non-epilepsy uses of antiepileptic drugs. *Pharm Rep* **58**: 1-12.

Zeilhofer H (2005). The glycinergic control of spinal pain processing. *Cell Mol Life Sci* **62**: 2027-35.

Zimmermann MB and Kohrle J (2002). The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. *Thyroid* **12**: 867-78.

Zucconi M, Coccagna G, Petronelli R, Gerardi R, Mondini S and Cirignotta F (1989). Nocturnal myoclonus in restless legs syndrome: effect of carbamazepine treatment. *Funct Neurol* **4**: 263-71.

Zucconi M, Ferri R, Allen RP, Baier P, Bruni O, Chokroverty S, Ferini-Strambi L, Fulda S, Garcia-Borreguero D, Hening W, Hirshkowitz M, Hogl B, Hornyak M, King MA, Montagna P, Parrino L, Plazzi G and Terzano MG (2006). The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med* **7**: 175-83.

Zwarts M and Stegeman D (2003) Multichannel surface EMG: basic aspects and clinical utility. *Muscle Nerve* **28**:1-17.